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INVESTIGATIONS ON THE CAUSES OF VACCINATION ENCEPHALITIS

BY

PROFESSOR A. ECKSTEIN.

(From the University Children's Clinic, Düsseldorf, Germany.)

The frequent occurrence of affections of the central nervous system following vaccinations has directed the attention of a wide circle of medical men in Germany to this disease. The two reports of the Vaccination Committee of the British Ministry of Health have contributed to clear up the character of the disease to a large extent. The investigations undertaken by the Dutch Ministry of Health showed very similar results and extended our knowledge of this peculiar disease. In Germany great

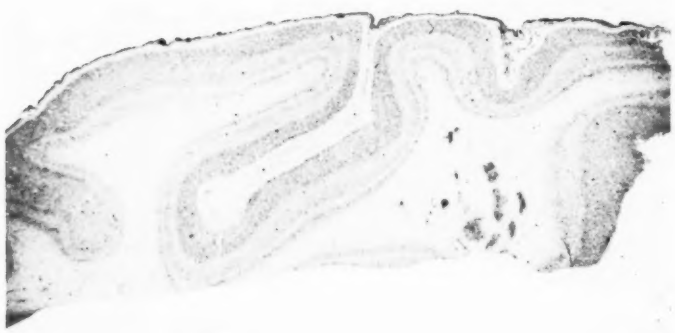

FIG. 1.—Perivascular infiltration of the medulla in human vaccination encephalitis (× 8).

difficulties were encountered in gathering facts regarding these cases, as the Committee appointed by the President of the Ministry of Health failed to reach a large number of the patients and subject them to suitable investigation. A survey of affections of the nervous system brought to the notice of the Ministry of Health as a result of prophylactic small-pox vaccinations undertaken from 1927 to 1930, and passed on to the Committee of Inquiry (Eckstein, Gildemeister, Gins, Manteufel, Noeggerath, Pette) for further examination, comprised 102 cases, of which 77 (25 fatal) in first vaccinations and 4 (all fatal) in revaccinations were recognized to be definite affections of the nervous system following small-pox vaccination or coming under consideration under this head as probable or doubtful cases. When compiling the list a distinction was made between encephalitis and other affections of

the nervous system following vaccination, such as meningitis and myelitis. In each of these two groups a distinction was also made between cases which were diagnosed by dissection, those clinically verified, and those which were probable, doubtful, to be declined, or unsuitable on account of lack of sufficient data. The compilation is as follows (Table 1):—

TABLE 1.

CLASSIFICATION OF CASES.

Year	First vaccination or re-vaccination	Post-vaccinal encephalitis				Other affections of the nervous system following vaccination				Cases to be declined	Unsuitable Cases
		Diagnosed by dissection	Clinically verified	Probable	Doubtful	Diagnosed by dissection	Clinically verified	Probable	Doubtful		
1927	First vaccination ...	2 (2)	7 (2)	2 (1)	—	1 (1)	1 (-)	—	—	1 (2)	1 (1)
	Re-vaccination ...	—	—	—	1(-)+ 1 (1)	—	—	—	—	1(-)+ 1 (1)	1 (1)
1928	First vaccination ...	2 (2)	16 (2)	2 (-)	2 (1)	1 (1)	2 (1)	—	—	—	—
	Re-vaccination ...	1 (1)	—	—	—	—	1 (1)	—	—	—	—
1929	First vaccination ...	6 (6)	13 (1)	2 (1)	1 (-)	—	3 (-)	—	1 (-)	2 (-)	2 (2)
	Re-vaccination ...	—	—	—	—	—	—	—	—	—	—
1930	First vaccination ...	—	7 (-)	—	1 (1)	2 (2)	—	2 (1)	1 (-)	5 (5)	6 (4)
	Re-vaccination ...	1(1)+ —	1 (1)	—	—	—	—	—	—	—	—
Total	First vaccination ...	10(10)	43 (5	6 (2)	4 (2)	4 (4)	6 (1)	2 (1)	2 (-)	8 (6)	9 (7)
	Re-vaccination ...	1(1)+ 1 (1)	1 (1)	—	1 (1)	—	1 (1)	—	—	1 (1)	1 (1)

+ Affections on which the Committee could not form an unanimous opinion.
( ) Number of deaths.

In 1931 56 cases were notified to the Committee of which 33 ended fatally. But the data on these cases were so vague that even now the Committee is unable to state which cases are to be attributed to vaccination alone.

In contradistinction to other European countries vaccination in Germany is even to-day still regulated by law. The Vaccination Law enacted in 1874 has not since been altered to any great extent. A 'conscience clause' which would give the possibility of breaking through the vaccination law has so far never been sanctioned, although it has been asked for in many quarters. An amendment not yet determined by law has been recommended by the Ministry of Health which is to the effect that enforced vaccination does not appear to be advisable and that any injury directly arising from vaccination

should be adequately indemnified. It was also suggested that in persons liable to receive vaccination who have suffered from acute infectious inflammatory diseases of the central nervous system, or still show sequelæ of such an affection, or whose relatives have suffered or are still suffering from such affections, vaccination should be postponed for at least one year. If requests are made to postpone vaccination more than twice, or in single cases for more than two years, the decision of the public vaccinating officer should be sought.

The vaccination technique which consists in making 4 incisions has not been altered, but in Germany 1 or 2 incisions are frequently made, as according to the regulations of the Vaccination Law vaccination is considered successful if one pustule arises. Moreover, only calf lymph which does not exceed a certain titre (1 in 10,000) is used for vaccination.

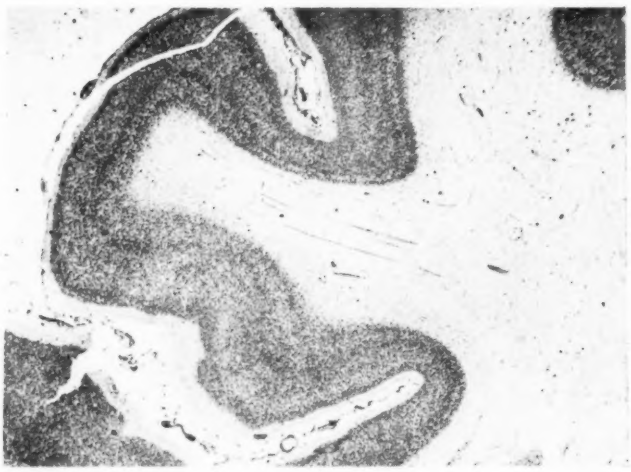

FIG. 2.—Perivascular infiltration of the medulla of a monkey with vaccination encephalitis (× 6).

On account of the support given us by the Ministry of the Interior, we, in conjunction with Hedwig Herzberg-Kremmer and Kurt Herzberg, were in a position to carry out clinical and animal experiments with a view to determining the course of vaccination and any injury to the central nervous system caused by the vaccine, which could provide fresh points of view for forming an opinion on vaccination encephalitis.

We succeeded in proving that even in normal persons the vaccine virus could be demonstrated in the blood with great regularity. These findings have since been confirmed by Gildemeister and Heuer. In these experiments we made use of the experiments of Othawara who after normal vaccination could demonstrate the vaccine virus in the blood by its retention in the testicle of a rabbit. The blood of most of the patients was positive between the third and tenth day, especially between the sixth and eighth day after vaccination, also when the clinical manifestations were present.

Although the view expressed by Pirquet—that vaccination represents a local process accompanied by a secondary allergic reaction—was, considering certain abnormal vaccination reactions especially of general vaccines, not probable, and although the acquisition of a general immunity following vaccination was rather in favour of a general infection of the organism with vaccine virus, only our experiments on a larger material of normal vaccinated children definitely proved this point. The occurrence of these general infections, especially affections of the central nervous system following vaccination, has a certain importance as they find their analogues

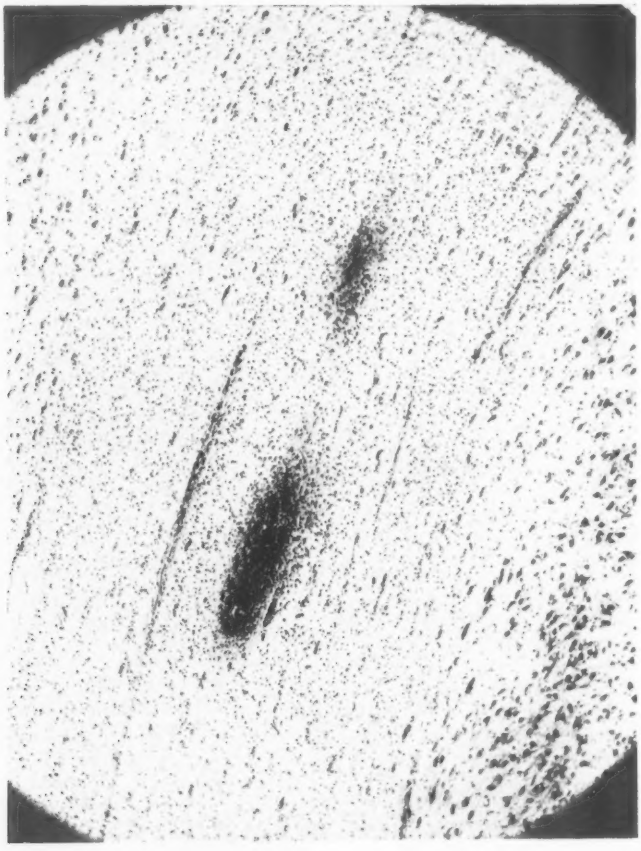

FIG. 3.—Perivascular infiltrations and hyperplasia of neuroglia in the medulla in human vaccination encephalitis (× 60).

in numerous other infectious diseases. This view was also confirmed by our further observations that in no case of normal vaccination did we succeed in proving vaccine virus in the cerebrospinal fluid, whereas in 5 cases of vaccinal injury of the central nervous system it could be demonstrated. Similar observations were also made by Altershoff, Gildemeister and Huber. In one case, by intra-cerebral vaccination into a rabbit of cerebrospinal fluid from a child suffering from post-vaccinal encephalitis Herzberg was able to produce an encephalitis,

There are two important points of view as to the causes of nervous complications following vaccination: (1) that the complications are due to an activation of the latent encephalitic germs caused by vaccination, or (2) that the vaccinations themselves are the cause of the complications. The ' activating theory ' has hitherto not provided any definite clues to go upon.

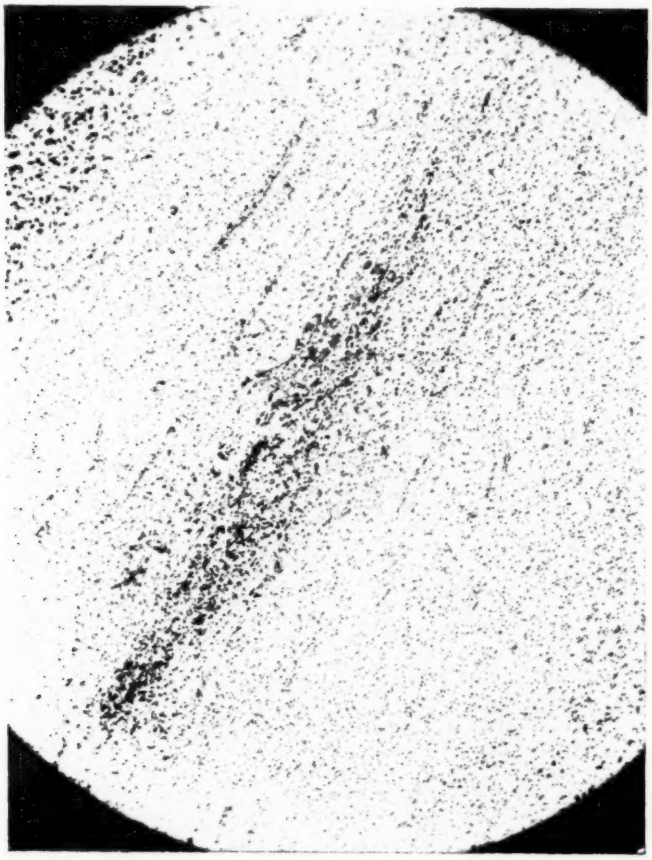

FIG. 4.—Perivascular infiltration and hyperplasia of neuroglia in the medulla of a monkey with vaccination encephalitis (× 62).

Also the typical experiments carried out by Pette on rabbits, to which reference is frequently made, were not conclusive. In these animals suffering from a bifid flora (B. bipolaris) of the naso-pharynx produced by vaccination died of bifidus sepsis (bipolaris) without showing any encephalitic symptoms. Similar experiments carried out by Bürger and his associates resulted in a negative finding. By excluding these possibilities the view gains ground that the vaccine virus itself is to be regarded as the actual cause of the complications. Our clinical observations mentioned above are in favour of this theory. In further experiments on monkeys we were able to demonstrate that the presence of vaccine virus in the blood (also

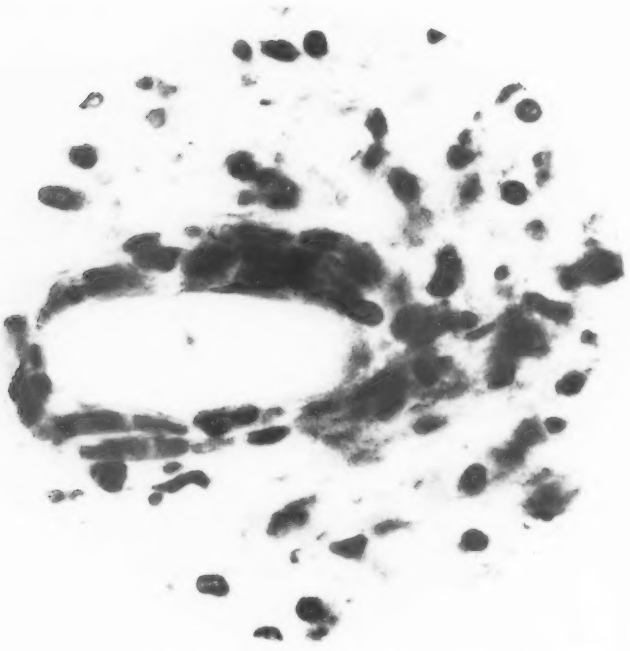

FIG. 5.—Blood vessel with infiltration macrophages and hyperplasia of neuroglia: human (× 720).

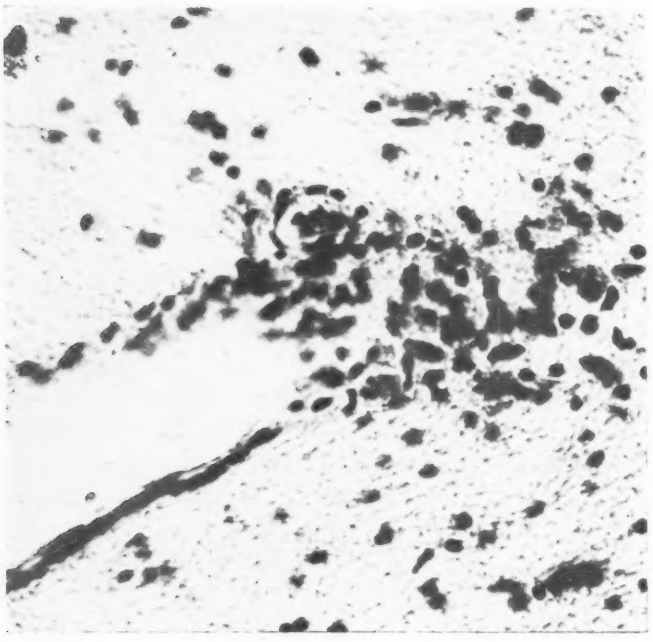

FIG. 6.—Infiltration macrophages and hyperplasia of neuroglia in monkey vaccination encephalitis (× 476).

by directly injecting large quantities of the vaccine virus into the blood-stream) did not give rise to any nervous affections as long as the barrier between blood and cerebrospinal fluid, as well as between blood and brain, is still intact. On the other hand, the presence of vaccine virus in the cerebrospinal fluid, also in very great dilutions, is connected with a meningo-myelo-encephalitis running a typical course. In other experiments by producing different degrees of disturbance of the circulation of the central nervous

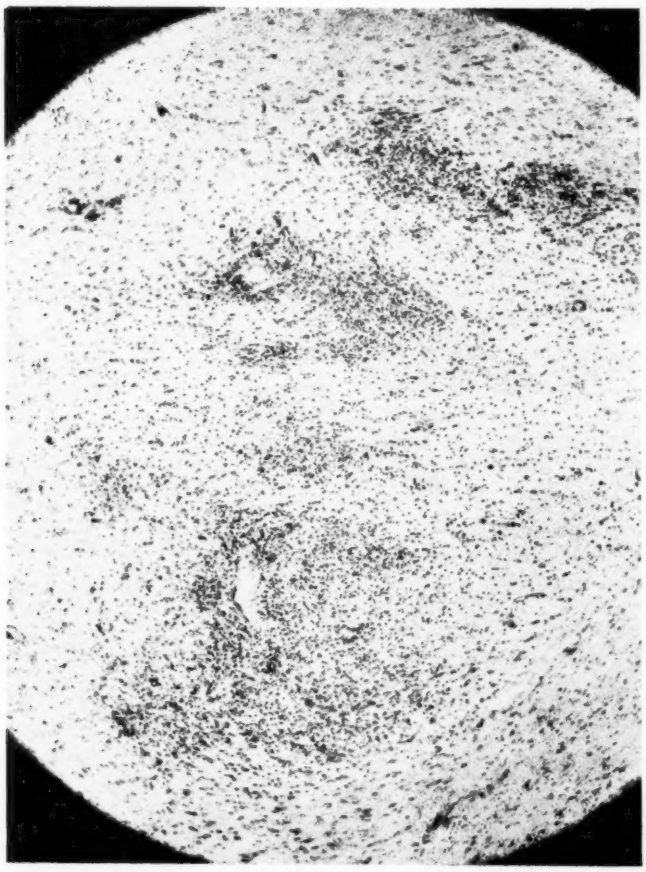

FIG. 7.—Perivascular infiltrations and patches of glia in the medullary substance of the cerebrum: human (× 61).

system (unilateral ligature of the jugular vein, transitory diathermy of the brain), and by simultaneously introducing the vaccine virus into the blood, we also succeeded in producing symptoms in monkeys which had a great clinical and morbid anatomical similarity to the so-called vaccination encephalitis observed in human beings. We obtained the same result by disturbing the current of cerebrospinal fluid by continuous lumbar punctures. A certain relationship may be found to the investigations undertaken by

Jowelews who used Speransky's ' pompage ' method and was able to produce the hydrophobia virus in the brain of rabbits. In one experimental animal which had been treated with diathermy, there existed in addition to the vaccination encephalitis a generalized vaccinia of the skin in the region of the diathermy (corresponding to an observation made by Weichsel in a case of vaccination encephalitis).

As the experiments were carried out with a standardized (human) vaccine which was always previously tested as to its sterility, here only the vaccine virus comes into consideration as the injuring agent.

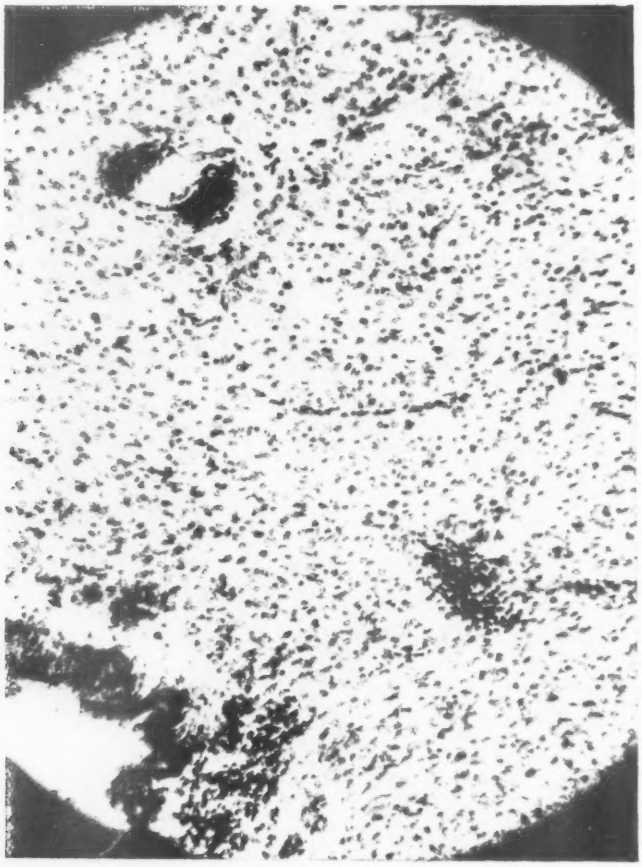

FIG. 8.—Perivascular infiltrations and hyperplasia of neuroglia in the neighbourhood of the ventricle in monkey vaccination encephalitis (× 150).

When trying to form an opinion as to the cause of vaccination encephalitis in human beings, attention was drawn over and over again to the fact that only in isolated cases has it been possible to prove vaccine virus in the brain of patients who died of vaccination encephalitis. But this proof loses its conclusive force in so far as the presence of vaccine virus in the blood is normal during the period in question and therefore should, of course, not be looked upon as being pathogenic in the brain.

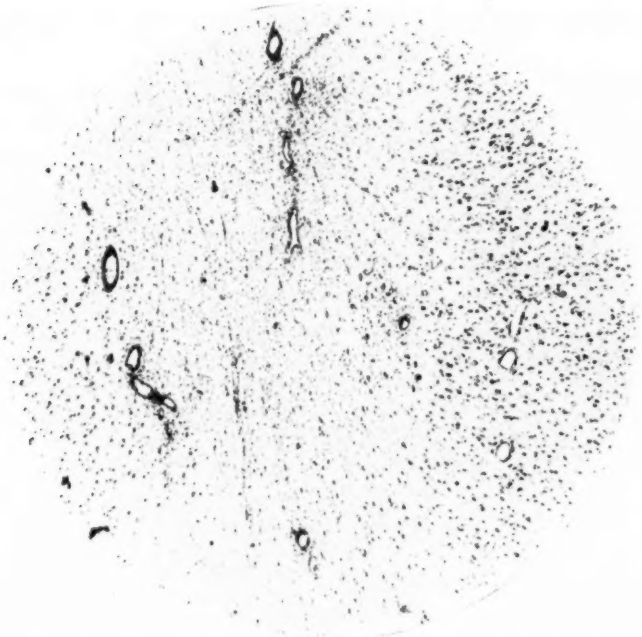

FIG. 9.—Disseminated foci in the medulla of the insula (island of Reil): human (× 35).

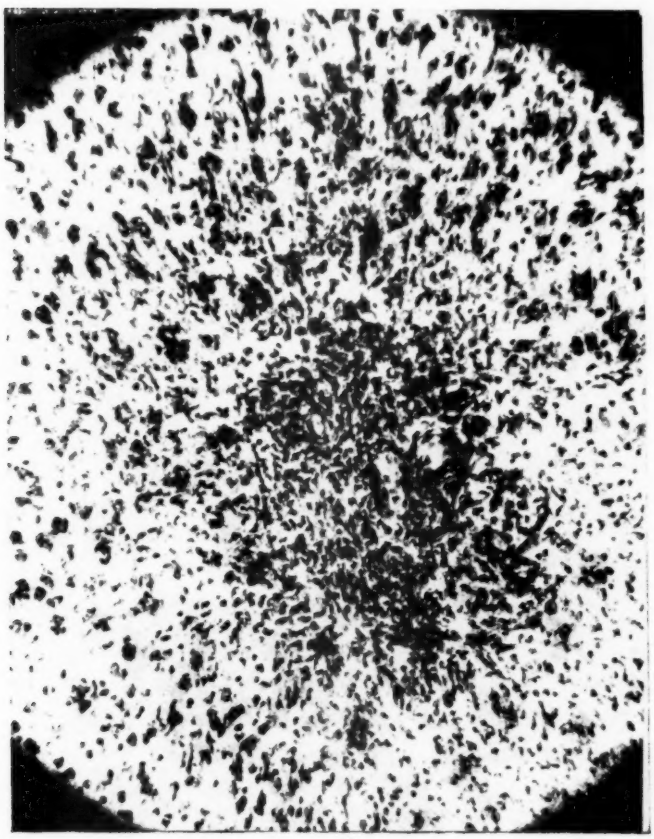

FIG. 10.—Perivascular infiltration in monkey vaccination encephalitis (× 147).

This question was also cleared up by experiments carried out by Herzberg. He was able to furnish proof that in the majority of cases a condition of self-sterilization exists at the moment of death which prevents vaccine virus from being demonstrable. In experiments on animals (rabbits), by giving direct cerebral injections and gradually increasing the massiveness of the infection, he succeeded in proving that from a certain limit onwards the animals show a protracted course of the disease which nevertheless ends fatally with symptoms of meningo-encephalitis. In animals

FIG. 11.—Marked meningeal reaction in vaccination encephalo-meningitis: human (× 61).

which died at a later period with characteristic symptoms vaccine virus could no longer be demonstrated, in contradistinction to those animals which died after a few days with very marked symptoms. The animals therefore died of the consequences of the nervous complications after the virus itself had meantime been destroyed. These vaccination tests explain satisfactorily the failure to find the virus in the brain of patients suffering from vaccination encephalitis.

The only question still to be cleared up is why certain individuals are affected by nervous vaccination complications, whereas in thousands of children who have been vaccinated with the same lymph vaccination runs a normal course. Cases should not be included for consideration when many other children living in the same district fall ill at the same time, e.g., the outbreak in 1930 in Stubaital (Tirol). In this large epidemic of cases showing nervous complications of vaccination, Reich was able to prove that children not vaccinated but living in the same district were also attacked by encephalitic symptoms. Here a local encephalitis epidemic is obviously present, the occurrence of which is not to be ascribed to vaccination.

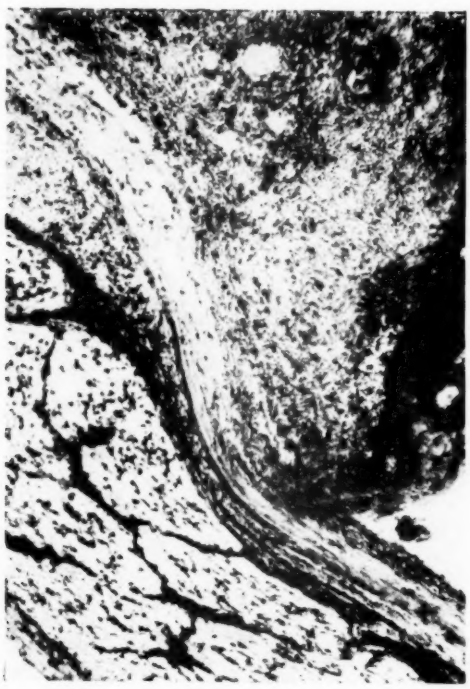

FIG. 12.—Meningeal reaction in monkey vaccination encephalitis (× 129).

However, most of the instances of nervous vaccinal complications recorded are isolated cases. In normal vaccinated persons permeability is not increased, as I was able to convince myself with the aid of Walther's bromine method: therefore an individual disposition to such disturbances must exist. This individual disposition, the constitutional factor of which displays itself in the occasional occurrence of nervous vaccination complications among brothers and sisters, is after all assumed for all nervous affections of the central nervous system. The affection of the central nervous system following vaccination would, therefore, also confirm our observations in this direction.

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AMYOPLASIA CONGENITA

(Multiple congenital articular rigidity : Arthrogryposis multiplex congenita)

BY

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(From the Hospital for Sick Children, Great Ormond Street, London.)

Under the names ' multiple congenital articular rigidity ' and ' arthrogryposis multiplex congenita ' a rare but well-defined clinical condition has

FIG. 1. X-ray of author's case in utero, showing extended position of the legs and arms. The fœtal bones have been slightly retouched.

been described, the characteristic features consisting of immobility of one or more joints of the limbs, generally symmetrically distributed, and dating

from intra-uterine life. The immobility may be absolute, or movement may be severely limited. The fixation of the joints has the clinical appearance of fibrous ankylosis, but there is no evidence of inflammatory change to account for this, and it would appear more probable that the condition depends primarily upon some developmental defect. In this connexion, the incomplete development, or even entire failure of development, of certain groups of muscles in the limbs, which has been recorded in cases specifically examined from this point of view, has been a striking feature.

FIG. 2. Patient aged 4 months: showing the characteristic position of the arms and legs.

Case report.

The patient, a girl, is the third and last member of the family. Her parents are healthy, as are her two brothers.

The medical history of the child begins when she was a seven months fœtus. She was at that time lying in a breech presentation position in utero, and an unsuccessful attempt was made under anæsthesia to turn her. An X-ray photograph of the mother's abdomen at that time (Fig. 1) shows the fœtus to be lying as a breech with extended legs, and the elbows can be seen to be extended, which is an unusual attitude. The child was born at full term as a breech with extended legs and extended arms. My thanks are due to the obstetric authorities at St. Bartholomew's Hospital for these ante-natal notes and the X-ray photograph.

The baby when nine weeks old was taken to the Orthopædic Department of St. Bartholomew's Hospital, and I am indebted to Mr. Elmslie for allowing me to quote the clinical condition noted at that time. The knees and elbows were rigidly extended, and could not be bent even under anæsthesia. The shoulders could be abducted to a right angle, and the wrists and fingers were held in flexion. The hip movements were fairly free. A diagnosis of ' congenital maldevelopment of joints ' was made.

The child first came under the present author's care at the age of 10 weeks, when the remarkable fixation in extension of the elbows and knees was noticed (Fig. 2). Scarcely any movement was possible in these joints. Since that time the child has been under constant supervision. No treatment has been given except that carried out by the mother, which has consisted of regular daily attempts to obtain passive movements of the fixed joints. A definite improvement has occurred in both knees and to a slight extent in the right elbow, but even so the clinical features of the case remain as clear now as when first seen.

FIG. 3. Patient aged 2 years : showing the free mobility of the spine, and the rigidity of the elbow.

Examination at the present time (patient aged 2 years) shows a well nourished child, weighing 27 lb. There are three nævi, one on the cheek, one on the back, and one on the left elbow, which have been successfully treated by freezing with CO_2 snow. There is nothing abnormal in the thorax or abdomen. The skull and spine are normal, and the movements of the spine and jaw are not diminished (Fig. 3). Owing to the nature of the deformities the tendon reflexes cannot be obtained, but there is no sensory loss nor trophic disturbance. Mentally the child is a normal and happy little girl, and is beginning to say short sentences.

UPPER LIMBS.—The principle features of the upper limbs are that the elbows are constantly held in rigid extension, the forearms are fully pronated, and the wrists flexed.

At the shoulders all movements can be performed, but abduction is carried out slowly and with obvious difficulty. Much of the shoulder movement depends upon the mobility of the scapula, and when this bone is prevented from moving, abduction of the shoulder is only possible to about 45 degrees.

At the elbows the child cannot herself perform any movements, but passively both joints can be flexed through about 15 degrees. When this limit of flexion is reached, the movement suddenly checks, as happens in fibrous ankylosis. The forearm is generally fully pronated, but can be semi-supinated. Further supination is impossible. The wrists are generally flexed, but flexion is incomplete and can only be carried through about three-quarters of the normal range. The child

FIG. 4. X-ray of patient's arm, to show the muscle outline. The bones appear normal. Compare the muscle outline with that of a normal child (Fig. 5).

FIG. 5. X-ray of the arm of a normal child, aged 2 years (same age as patient) to show the muscle outline.

manages to extend the wrists until the hands are in a straight line with the forearms, but cannot cock the wrists. The fingers and thumbs can be moved normally.

The arms have a peculiar shape, for they taper from the wrists up to the shoulders, where the circumference of the arms is least. The appearance suggests

that the shape of the arms is due to œdema of the subcutaneous tissues, becoming more marked towards the wrists; and that some such condition may actually be present is further indicated by the absence of the normal bony contours round the elbows and wrists. There is, however, no pitting, and the nutrition of the arms as judged by their colour and warmth seems normal. There is a small dimple in the skin over the back of the styloid process of the ulna. It affects the skin only, and can be picked up and obliterated, and moved freely over the underlying structures.

X-ray examination of the bones of the upper limbs shows no abnormality of bony outline, and the bones are well calcified and appear strong. The loss of joint movement cannot be attributed to deformity of the bones.

The muscular condition of the arms has been investigated by taking ' soft ' X-ray photographs, which indicate clearly the muscular masses, and also by testing the electrical reactions. The X-ray appearance of the arm muscles is shown in Fig. 4, which should be compared with Fig. 5 showing a similar picture of the arm muscles of a normal child of the same age. The deltoid muscle of the patient is greatly diminished, appearing like a thin strap overlying the shoulder joint. The X-ray opacity of the muscles surrounding the shaft of the humerus is also much diminished and the breadth of the muscle shadow is reduced, but in the X-ray the triceps and biceps cannot be distinguished clearly from each other. The muscle opacity in the patient's forearm compares favourably with that of the control.

The electrical reactions to faradism were kindly tested for me by Dr. Clayton at King's College Hospital, and the results from the arm muscles are set out in Table 1 (p. 135). The following muscles gave no response at all :—the biceps, supinator longus, and extensor carpi radialis longior; the reaction of the deltoid was very weak. It may be pointed out here that the muscles which are affected are precisely those that should produce the movements which the child is unable to perform. The muscles which give a normal faradic response are those which, if actin" unopposed, would place the limb in the position in which we find it; these muscles do not show hypertrophy or hypertonus so that the position of fixation of the joints, while due perhaps to the unopposed action of these muscles, is not attributable to any muscular overaction. Indeed it is likely that these unopposed muscles have, owing to lack of antagonistic action, undergone some secondary atrophy.

Lower Limbs.—The lower limbs are maintained in an attitude of rigid extension of the knees, with bilateral talipes equinus.

The buttocks are firm and the gluteal muscles well developed. All the hip movements are easily carried out through a full range. At the knees the range of movement has increased since birth, at which time the joints were rigidly extended and flexion completely impossible. At the present time the right knee can be flexed to a right angle, and the left knee moved through about three-quarters of a right angle. The amount of active movement in the knees is a little less than can be obtained passively. During movements some fine creaking can be felt in both joints. When the limit of flexion has been reached, movement is suddenly checked as in a fibrous ankylosis.

Movement at the ankles is considerably limited, and the position of talipes equinus is associated with some shortening of the tendo Achillis. The toes are not moved voluntarily, but passively they can be fully extended.

The contour of the legs is almost as striking as that of the arms, for they taper steadily from the upper part of the thighs to the ankles. There is no bulge of calf muscles. On the lower part of each leg is a symmetrical groove in the skin, beginning over the mesial aspect of the tibia at the junction of its lower third and upper two-thirds, and running downwards and slightly outwards across the middle of the front of the ankle to end just to the outer side of the middle of the dorsum of the foot. These grooves are only skin deep, and can be moved independently of the underlying structures. They do not correspond to the direction of the tendons

of the anterior tibial or peroneal groups of muscles. Actually no tendons can be seen or felt crossing the front of the ankle. The appearance of œdema is not so noticeable in the legs as in the arms, but the bony prominences and hollows on either side of the patellar tendon are obliterated, and the knees appear as smooth spindle shaped swellings breaking the otherwise even tapering of the legs.

FIG. 6. X-ray of patient's legs, to show the muscle outline. The bones appear normal. Compare the muscle outline with that of a normal child (Fig. 7).

The X-ray outline of the bones of the legs is normal. There is perhaps a slight reduction in the joint space of the knees, the tibia and femur appearing a little closer together than in the normal, and the fibula seems to be displaced slightly backwards on the tibia, so that in the antero-posterior view these bones appear closer together than normal.

X-ray investigation of the muscles of the lower limbs (Fig. 6 and 7) shows a considerable reduction in the amount of muscle surrounding the femur, and in a lateral view this deficiency is seen to affect chiefly the hamstrings. Below the knee there is nothing to be seen of the anterior tibial or peroneal groups; the gastrocnemii are reduced in size, and can be seen as a short tag on the inner side of the top of

FIG. 7. X-ray of the legs of a normal child (same age as patient) to show the muscle outline (cf. Fig. 6).

the tibiæ. The capsule of the knee-joint does not appear more dense than in the normal leg.

The faradic reactions of the leg muscles are recorded in Table 2 (p. 135). The reaction from the hamstring muscles was noted as very weak, and no response was obtained from the anterior tibial or peroneal groups. As in the arm, so in the leg, the muscles which are affected are precisely those that should give rise to the

movements which the child cannot perform. It is also curious that in the upper and lower limbs the affected muscles have corresponding functions; the flexors of the elbow and knee are either very deficient or absent, while the extensors of the wrist and ankle are also picked out.

In case there should be an element of spasm accounting for the limitation of joint movement, the child when 2 years old, was examined under an anæsthetic, but no increase of mobility was obtained. This confirmed the result of a similar examination made when the child was 6 weeks old.

The effect of the rigid joints on the child's activities is severe. She is unable to feed herself in the ordinary way, and until now the mother has had to give the child all her meals. Instead of being able to crawl on her hands and knees, the child manages to move about on her feet and knuckles, the arms and legs being of course rigidly extended. At the present time she is just beginning to walk alone, making use of slight flexion of her knees. When standing, she bends forwards at the hips, counteracting this by an excessive lumbar lordosis.

SUMMARY.—The case recorded is that of a child aged 2 years, who from birth has suffered from rigid extension of the elbows and knees, and limitation of movement in the shoulders, wrists, and ankles, inability to pronate the forearms, and bilateral talipes equinus. The condition is of prenatal origin, bilateral and strictly symmetrical. The bony skeleton and the joint contours are normal. The range of movement of the affected joints is suddenly checked, simulating fibrous ankylosis, and indicating undoubted intrinsic changes within the joints. Finally, there is great diminution of some muscle groups in the limbs, and complete absence of others. This muscular defect is symmetrical, and the affected muscles are those which should normally give rise to the very movements which the child is unable to perform.

Discussion.

Previously recorded cases.—The literature on the subject of this disease is scanty, and practically all examples have been recorded by orthopædic surgeons, to whom, as might be expected, these cases gravitate.

The most comprehensive paper is one written by Rocher[1] in 1913, based on four personal cases and 26 instances collected from the literature. He employs the descriptive name of ' multiple congenital articular rigidities,' a name first given to this condition by Nové-Josserand. A description of Rocher's various cases will not be given here, but his clinical account and the photographs of his cases leave no doubt that the condition he describes is identical with that here recorded. Of his cases in which the sex of the child was mentioned, 15 were boys and 7 were girls, but the figures are too small to indicate whether there is any sex predominance. The condition does not appear to affect particularly first-born children, and from the family histories there is no hereditary or familial tendency.

Rocher points out that although the rigidity is generally bilateral and symmetrical, it may affect only one joint, or the joints of one limb, or the position in which fixation occurs may differ in corresponding joints of two limbs. He describes the three following clinical types:—

1. Fixation of all four limbs in extension. This is the most frequent type, and the case recorded here is a typical example.
2. Fixation of the knees in flexion, sometimes combined with fixation of the hips in flexion and abduction.
3. Fixation of one elbow in extension, and the other in flexion. In this type the legs may be fixed in extension.

It seems likely that fixation of the joints may occur in almost any combination, both as regards the number of joints involved, and in their position.

Rocher's analysis of his cases shows that in the first clinical type the shoulder joint is likely to be stiff, and its movements limited. The elbows are fixed in extension, the wrists are stiff and extension is limited, and the fingers are commonly in the position of a 'claw-hand.' Pronation and supination can only be partially carried out, and there may be subluxation of the upper end of the radius. With regard to the muscles, the deltoid is considerably atrophied and may be absent, and the same may be true of the biceps; the triceps is on the contrary well developed. The extensor muscles of the forearm are poorly developed, while the flexors of the wrists and fingers are generally normal. Shortening of the flexor tendons of the fingers has been recorded as in Volkmann's ischæmic contracture, flexion of the fingers being more easily performed when the wrists are also flexed.

The position of the lower limbs varies with the clinical type to which the child belongs. The hips may be rigidly fixed in extension, or flexion, or flexion with abduction as in the squatting position. The attitude at the hips may be only temporary or may persist. Congenital dislocation of one or both hips has been recorded as a complication.

The knees may be fixed in flexion or extension. Fixation in extension allows of flexion taking place up to a right angle; fixation in flexion may be so severe that the feet are pressed against the buttocks. Creaking can often be felt in the knees during passive movements. The feet are generally clubbed.

With regard to the muscles of the lower limb, when the knees are fixed in extension the hamstring muscles are under-developed, while fixation of the knees in flexion is accompanied by aplasia of the quadriceps. In both positions the patella is often abnormal, being displaced, small, or even absent.

The muscles never show a reaction of degeneration, so that the muscular atrophy is probably not of nervous origin, but the reactions to faradism and galvanism are diminished or absent, indicating hypoplasia or complete aplasia of muscle. There are no sensory or trophic changes. The tendon reflexes are naturally difficult to obtain, but when present they are not increased. The normal intelligence of the children is commented upon.

Rocher has also pointed out the thickened appearance of the subcutaneous tissues obliterating the normal bony landmarks round the knees and elbows, and states that this 'fatness' may be lymphangiectatic in origin. In a case recorded by Magnus[2], this subcutaneous thickening was missing, and the muscular aplasia was so great that the child appeared to be simply skin and bone. Rocher also draws attention to the little dimples in the skin over the styloid process of the ulna or on either side of the patella. Lastly, this author states that there may be some shortening of the affected limb or segment of a limb. Of associated conditions there may be ankylosis of the mandible, and some vertebral stiffness or scoliosis.

In 1928 Rocher[3] recorded two more cases. One was a child, 12 years old, with rigid extension of the arms and flexion of the knees: the other aged 6 months with rigid hips and knees. In 1930 the same author with Ouary[4] described two additional cases. In one the arms were fixed in extension, with bilateral talipes; in the other, a girl aged 3 months, there were fixation of the legs in extension and double talipes, associated with several malformations of the lumbar vertebræ and aplasia of the sacrum.

Another case was recorded by Marconi[5] in 1922, and in 1926 Scarlini[6] gave an account of three cases that had been under his care. The first of these was a girl aged 7 years with elbows fixed in extension, limitation of abduction of the shoulders, and fixed flexion of the knees. A point of interest in the history of this case was that the mother did not experience quickening until the sixth month of pregnancy and fœtal movements soon faded away entirely. The other two cases were boys aged 22 months and 7 years respectively, both of whom suffered from bilateral rigidity of the knees in full flexion. In each case the arms were unaffected. Scarlini added that the rigidity of the joints was not due to bony deformity as judged by clinical and radiological examination, but he considered musculo-ligamentous retraction to be the cause, and he confirmed Rocher's observation that the electrical reactions of the muscles are much diminished, without showing a reaction of degeneration.

In 1923 Stern[7] summarized four cases that had been under his care, and gave to the condition the name ' arthrogryposis multiplex congenita.' In his cases there was limitation of movements of all joints except of the mandible and spine. The limitation was typical in that movement was possible for a few degrees, and then both active and passive movements were impossible. He pointed out that there was no malformation of the joint surfaces, nor congenital contracture of muscles or tendons. One case had a congenital dislocation of the hip, and another a subluxation of the tibia. Dimpling of the skin over the elbows and patellæ was noted. He commented upon the poor development of the muscles of the limbs, but ascribed this to the lack of joint movement, and a closer enquiry into the various muscle groups was not recorded.

Two years later Lewin[8] recorded two cases in babies of 6 weeks and 14 months of age. He followed Stern in employing the name of ' arthrogryposis multiplex congenita.' In his cases the arms and legs were involved, the knees being fixed in flexion and the hips in abduction, so that the legs formed a diamond-shaped figure.

In addition to these cases from the literature, brief clinical notes of four cases which have been under the care of my colleague Mr. Fairbank are presented, as they are undoubted examples of the condition. I am much indebted to Mr. Fairbank for giving me access to these cases.

(1) The first was a boy aged 3 months, in whom there was a congenital limitation of extension of the left elbow, the left hand being fixed in dorsiflexion with ulnar deviation. The right hand was fixed in palmar flexion with ulnar deviation.

The left hip was congenitally dislocated, the left knee was rigidly extended, and the left patella was absent. There was also bilateral talipes equino-varus (Fig. 8).

FIG. 8.

(2) The second case was a girl aged 1 year. She was the second child of the family, and the birth had been easy. Both elbows were fixed in extension, and there was some limitation of external rotation of the humerus (Fig. 9).

FIG. 9.

(3) The third case was a boy aged 22 months. The elbows and knees were fixed in extension, the wrists and hands were flexed, and there was bilateral talipes equino-varus. This child also had congenital dislocation of both hips (Fig. 10).

FIG. 10.

(4) The fourth case was a boy with severe congenital talipes equino-varus, associated with flexion and abduction of the hips and flexion of the knees. At the age of 4 years, the flexion of the knees was so extreme that the feet were folded against the buttocks, extension being impossible owing to contraction of the hamstring muscles. The flexion of the knees was partly reduced by means of wedge

plasters at a London hospital. Fig. 11 shows the condition of the legs when the boy was 6 years old, at which time he was admitted to Alton under the care of Sir Henry Gauvain. A series of corrective operations on the legs, including osteotomy

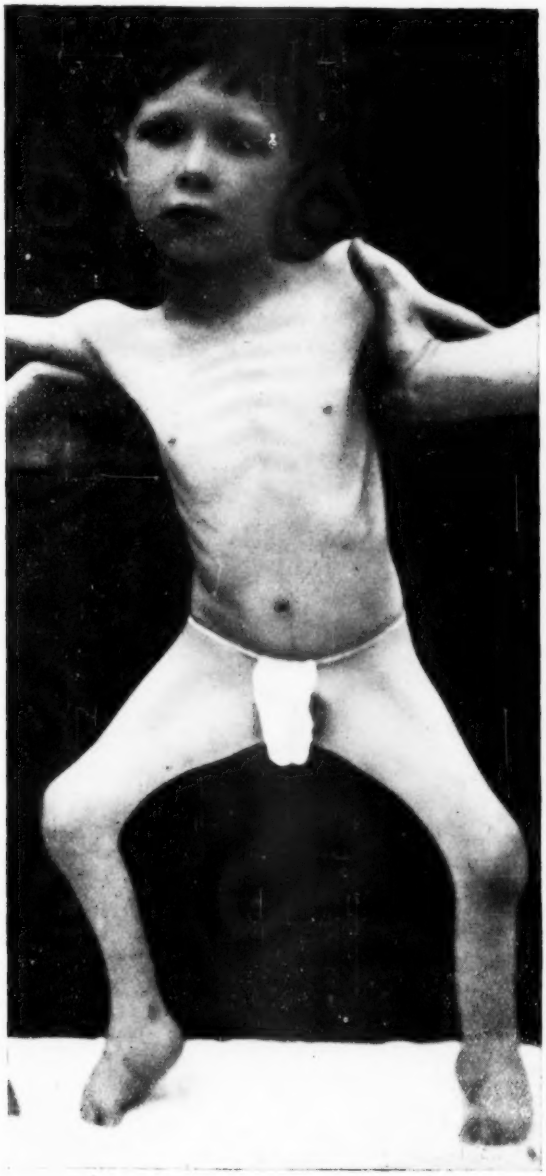

FIG. 11. Showing the position of the legs when the boy was six years old. The arms were unaffected.

of the femora and tarsal bones, was carried out by Mr. Fairbank, and the improvement which followed is shown in Fig. 12, when the boy was 10 years old. He was then getting about well in double calipers; there was still very little movement at the hips and knees, but there was no deformity of these joints. I am much indebted to Sir Henry Gauvain for allowing me to record this case.

A more detailed investigation of the muscles of these four children was not undertaken. These cases together with the first case recorded in this article and those already in the literature bring the total number up to 49.

FIG. 12. Showing the position of the legs at the age of ten years, after corrective operations. Compare with Fig. 11.

Pathology.—There have been no post-mortem examinations made on this condition, and therefore our knowledge of its pathology is scanty. X-ray studies show that the bones are unaffected, except that they may take part in the general shortening of the limb which Rocher has described. Congenital subluxation and dislocation of the joints, particularly of the hip joints, is not an infrequent complication, but is either a secondary or else concomitant

condition, since immobility also occurs when there is no dislocation. The internal anatomy of the affected joints has not been studied except that in one case of fixation of the knee it was noted that only that part of the femoral condyles which was in actual contact with the tibia was covered with cartilage; elsewhere the articular surface of the condyles was covered with fibrous tissue. Rocher states that there may be abnormal arrangement of the synovio-capsular apparatus. Congenital abnormalities of the lumbar vertebræ and aplasia of the sacrum have been reported.

Shortening of the tendons contributes to the deformity of some of the joints. In the first case recorded here, the tendo Achillis was shortened, and comment has been made upon the contraction of the flexor tendons which Rocher observed. He also adds that the skin may become contracted, as in one case of fixed flexion of the knee in which resection of the joint was performed. Before the limb could be straightened a plastic operation on the skin behind the knee was necessary.

Under-development or even absence of certain muscle groups is indicated by clinical, radiological, and electrical studies, but few observations on the muscles have been made. Rocher states that at operation the muscles appear pale, and when cut they retract but little.

Diagnosis.—The name ' multiple congenital articular rigidity ' sums up the leading clinical characteristics of the disease, and once seen the recognition of other cases should be easy. It is to be remembered that the position in which individual joints may be fixed may vary in different cases, as may the range of movement. The only other disease with which it might be confused is spastic diplegia due to lesions of the nervous system, but in that condition the stiffness of the limbs can be slowly overcome by passive means, and there is no actual fixity of the joints. Also the spasticity relaxes under anæsthesia.

Cases with fixed extension of the elbows, pronation of the forearms, and flexion of the wrists, bear a resemblance to Erb's type of brachial palsy, but in the latter condition the arms are flail, and there is no ankylosis of joints.

The rigidity is greatest at birth; it may persist undiminished, but by constant efforts at passive movements carried out over months or years, some increase in the range of mobility may be obtained. This has happened in the first case here recorded, and Stern reported that in one of his cases, passive movements led to a 25 per cent. increase of function. Major orthopædic operations have been undertaken in some of the cases with apparently good results, particularly in the cases of fixed flexion of the knees. In Scarlini's cases, osteotomy of the femur and tendon section rendered the children able to walk with the aid of splints.

Pathogenesis.—The cause of the deformities described is a matter of speculation, and it is quite likely that although these cases bear a clinical similarity to each other, more than one pathogenic process is involved. There is general agreement that the condition is present at birth, and has

originated during intra-uterine life: also that the loss of joint movement is not the outcome of bony deformity or bony ankylosis.

Stern and Lewin attribute the condition to intra-uterine inflammation and thickening of the periarticular tissues, with wasting of the muscles as a secondary phenomenon. However, from the history of the cases there have been no maternal illnesses which might lead to periarthritis in the fœtus, and the children after birth show no interference of function of their main viscera; in fact except for their remarkable limb deformities they seem to be quite healthy. It is also difficult to regard the state of the muscles as secondary to loss of joint mobility, for the distribution of the under-developed muscles is certainly not what would be expected to result from fixation of the joints. For instance, when the knee is fixed in extension, the quadriceps is well developed while the hamstring muscles are aplastic. Yet if in later life the knee is fixed in extension, as when the limb is put in plaster, we find that the quadriceps wastes more rapidly and to a greater extent than do the hamstring muscles. Stern also considers that the deformities are too symmetrical and regular to be attributed to abnormal embryonic growth; yet deformities of embryonic growth, such as are seen in achondroplasia or polydactyly, are usually bilateral and symmetrical. Scarlini does not deal with the ætiological aspect of the condition, which he admits is obscure, except to express his opinion that the cause does not lie primarily with the fœtus, but in some abnormality of the tissues or fluid surrounding the fœtus which prevents the normal growth of the limbs.

Rocher's view is that the initial trouble lies in abnormal compression of the fœtus, from which there follows a secondary defect of growth of all the structures which are concerned in the functioning of a joint—the bones, joint capsule, ligaments and muscles. He holds that the maldevelopment of all the tissues occurs simultaneously, and that no one tissue is primarily involved.

In the first place, what is the evidence of intra-uterine compression? Rocher lays stress on the history of oligamnios in a few of the cases. The nature of the birth is omitted in the majority of the histories, but details are obtainable in 18 cases. The labour was noted as difficult in two cases, and easy in six. Oligamnios occurred in four cases; but one of these was a fifth child, the other children being normal, although oligamnios was noted at each birth; and in another instance recorded by Scarlini the affected child was the third member of the family, the other two children being normal, and oligamnios had occurred at each birth. On the other hand, hydramnios was reported in two cases. It is difficult to see how fixation of the limbs could occur from compression in hydramnios, nor can it be presumed that unusual compression of the fœtus occurred where pregnancy and labour were normal.

If abnormal compression in utero were really of ætiological importance it is surprising that its effects are confined to the limbs, leaving the vertebral and cervical movements unimpaired; torticollis might also have been expected

to occur in some of the cases, and even evidence of pressure on the skull leading to abnormal shape, and possibly some degree of mental defect. On the whole, there seems to be no convincing evidence of abnormal compression of the fœtus in utero.

Rocher's second contention, that the defect of growth is applied simultaneously to all the structures concerned in the function of the joint, no one tissue being primarily affected, depends very largely upon the acceptance of abnormal intra-uterine compression as the origin of the condition. Such a view does not take into consideration what must surely be of significance, namely, that the aplasia of muscle is not evenly distributed among the muscles which surround the stiff joint, but picks out those by which the lost movements should be performed.

It seems likely that the peculiar distribution of the muscle aplasia is of considerable ætiological importance, and it may be that the interference with the development of the muscles is the primary lesion, to which the changes in the periarticular tissues are secondary. Some light may be thrown on this aspect of the condition by recalling the changes that take place when an ununited fracture goes on to the formation of a pseudarthrosis. In such circumstances the movements of the two fragments of bone on each other lead to a smoothing off of the bone ends, forming a shallow ball and socket joint; a joint capsule is fashioned from the surrounding fibrous tissue, while between the bone ends an adventitious bursa develops and acts as a synovial cavity. Reasoning from this, it may be supposed that in the growing limb bud of the fœtus, the movements of the segments of the limb, produced by the contractions of the muscles, aid in the natural formation of the structures of a joint, and that if the muscles are unable to move the bones, the differentiation of the joint structures will be incomplete. The manner in which deformity would thus be brought about may be illustrated from the first case in this paper. In the case, for instance, of the elbow, the triceps was well developed, but the biceps group (including the brachialis anticus) was under-developed, and probably absent. With only the triceps acting, the elbow would be constantly in extension, and the structures composing the elbow joint would be correspondingly incompletely developed. The capsule would become secondarily contracted, and probably too tight to allow of complete flexion, while if scarcely any movement at all was possible, the synovial lining might either be absent or its opposite layers be adherent to each other. Secondary changes such as these at the joints would account for the clinical appearance of fibrous ankylosis. The unopposed muscles would be likely to undergo secondary atrophy and shortening.

We have as yet no knowledge of the condition of the motor nerves to the affected groups of muscles, but the fact that a group of muscles having a common function is affected rather than individual muscles is perhaps a point in favour of attributing the condition of the muscles to a primary neurone defect, and in this connection it is interesting to note that the type

that has extended elbows and flexed wrists with limited abduction at the shoulder bears some clinical resemblance to Erb's brachial palsy due to lesions of the fifth and sixth cervical roots. On the other hand, there is no reaction of degeneration, sensation is unimpaired, and the general nutrition of the limbs is good. There is at present insufficient evidence to attribute the condition to a primary defect of the lower neurone.

The view expressed in this paper in explanation of these cases supposes that the initial defect consists of a developmental aplasia of certain groups of limb muscles. Following upon the aplasia of muscle, secondary developmental changes occur in and around the joints, leading to the clinical picture of fibrous ankylosis.

Nomenclature.—The term used by Stern and Lewin ' arthrogryposis multiplex congenita,' consisting as it does of a mixture of Latin and Greek, has little to commend it. Arthrogryposis means a bent or crooked joint, but the trouble in many of these cases is that the affected joint is persistently straight, and cannot be bent. The name also suggests that the condition is one primarily of deformed joints, and does not indicate the important changes in the muscles. Perhaps a stronger reason for rejecting this title is that ' arthrogryposis ' has been used in text-books on pædiatrics both in America and in Europe as a synonym for tetany. The following passage occurs in the 1922 translation by Sedgwick and Scherer[9] of Feer's ' Pædiatrics ':— ' Tetanic carpo-pedal spasms, or arthrogryposis, consist in peculiar tonic spasms of the hand resulting in the well-known ' obstetrician's hand '.' Arthrogryposis is similarly used in Holt and Howland's ' Diseases of Infancy and Childhood ' (1926)[10], and in Griffith and Mitchell's ' Diseases of Infants and Children ' (1927)[11].

The name ' multiple congenital articular rigidity,' used by Nové-Josserand, Rocher, and Scarlini, summarizes the principal clinical features by which the condition may be recognized, but gives no indication of the important changes in the muscles. It is likely that examples of this condition have also been described under other names, such as ' multiple congenital deformities,' and ' congenital malformation of joints.'

In the belief that the initial lesion is a primary aplasia or hypoplasia of certain muscle groups, the name ' amyoplasia congenita ' is put forward as conveying the origin of the condition.

Summary.

1. A case is recorded of a child with congenitally rigid arms and legs, associated with aplasia of certain muscle groups.

2. The literature of the condition is reviewed, and 44 cases are collected. In addition four cases under the care of Mr. Fairbank are added, bringing the total number of cases to 49.

3. The pathogenesis of the condition is discussed, and the view is put forward that the initial lesion consists of a developmental aplasia of certain muscle groups, followed by secondary developmental defects in the structure of the joints.

4. The names ' arthrogryposis multiplex congenita ' and ' multiple congenital articular rigidity ' are discussed, and the name ' amyoplasia congenita ' is preferred.

In conclusion, I should like to acknowledge my thanks to Mr. Fairbank for his helpful criticism in the preparation of this paper.

TABLE 1.

AUTHOR'S CASE OF AMYOPLASIA CONGENITA: ARM MUSCLE REACTIONS TO FARADISM.

Muscles.	Left arm.	Right arm.
Deltoid	Reduced	Reduced
Triceps	Normal	Normal
Biceps	Nil	Nil
Infraspinatus	Normal	Normal
Supinator longus and extensor carpi radialis longior	Nil	Nil
Extensors of fingers and thumb and extensor carpi ulnaris	Normal	Normal
Flexors of fingers and wrist	Normal	Normal

TABLE 2.

AUTHOR'S CASE OF AMYOPLASIA CONGENITA: LEG MUSCLE REACTIONS TO FARADISM.

Muscles.	Left leg.	Right leg.
Gluteus maximus	Normal	Normal
Quadriceps femoris	Normal	Normal
Hamstring muscles	Very weak	Very weak
Anterior tibial group and peroneal muscles ...	Nil	Nil
Gastrocnemius and long flexors of toes ...	Normal	Normal

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OSTEOPSATHYROSIS (Lobstein's Disease)

A CRITICAL REVIEW

BY

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The disease of which an illustrative case is reported below was first described in 1833 by Lobstein[27], who gave it the name of ' osteopsathyrosis ' (ὀστέον = a bone, ψαθυρόν = friable). According to his original description it is characterized by the appearance in certain families of cases of undue fragility of the bones. This fragility manifests itself in a tendency of the bones to break as the result of slight violence. On the other hand, repair of the fractures takes place not less rapidly than in normal bones.

Since the publication of Lobstein's work many other cases of the disease have been recorded, and a clinical picture has gradually emerged in which fragility of the bones appears as one of a group of associated abnormalities. Many of these are exemplified in the case now to be described.

Case report.

The patient, a married woman of 35, came to the New Sussex Hospital complaining of curvature of the spine, present since the age of 10 years, and of pain in the back for the last few months. She stated that since the birth of her only child, 5 years ago, she has noticed that her eyes were getting blue. This blueness is said by her sister, however, to have been present for at least 8 or 10 years. Four years ago she began to be deaf in the right ear, as the result, she thought, of a cold. She was treated by politzerization but the deafness was not relieved. It grew gradually worse, and the left ear began to be affected. Ringing noises were noticed, first in the right ear and later in the left ear also. She broke her left humerus at the age of 12 years, from a fall while jumping at school, and shortly afterwards broke the left ulna twice in succession from falls in the school playground.

PHYSICAL EXAMINATION.—Patient is a small woman (about 5 ft. in height), healthy looking and (for her size) of fair muscular development. She is so deaf that the voice must be raised in speaking to her. The scleræ are of a moderately deep indigo blue colour, and each cornea shows a well-marked arcus senilis. The upper teeth are false. The lower incisors are small and thin, and the enamel worn away towards the free edge, which has a mouse-eaten appearance. The remaining teeth appear normal. There is a severe structural scoliosis (single curve, convex to the left, apex at the 10th-11th dorsal vertebra). The limbs are of normal length and the long bones show no abnormal curvature. The shape of the skull is not suggestive of ' crâne à rebord.' There is slight hyperextensibility of the fingers. Routine examination of chest and abdomen reveals nothing abnormal.

X-RAY EXAMINATION.—The following bones were examined: skull, spine, pelvis and the long bones of both upper and both lower limbs. The vertebræ show the ordinary scoliotic changes. There is a slight irregularity of the lower end of the left humerus, at the site of the former fracture. An exostosis is present at the upper end of the right fibula. With these exceptions the bones, which are of slender build, show nothing abnormal in form or structure. There is no evidence of otosclerosis in the plates of the skull, nor of arteriosclerosis in any of the plates. There is well-marked calcification of the laryngeal cartilages.

HEARING.—Otological examination by Mrs. Logan yielded the following results:—

R. ear: Rinné negative. Meatus: 256 D.V. minus 20 sec.
512 D.V. ,, 60 sec.
Mastoid: 256 D.V. indistinguishable from own tinnitus.
512 D.V. minus 15 sec.

Mixed deafness, but tending to be more labyrinthine than obstructive.

L. ear: Rinné positive/negative. Meatus: 256 D.V. minus 20 sec.
512 D.V. ,, 10 sec.
Mastoid: 256 D.V. ,, 50 sec.
512 D.V. ,, 10 sec.

Meatal hearing and mastoid hearing are equally impaired.

BLOOD.—Calcium content of serum 10·2 mgrm. per cent. Wassermann reaction negative.

FAMILY HISTORY.—The patient states that 'blue eyes' have occurred frequently in her family on the mother's side. The earliest case known to her is that of her mother's mother, who was also deaf. This grandmother was the second child in a family of three. The eldest (♀) also showed 'blue eyes' and deafness, and the youngest (♂) was deaf. None of these people is known to have had a fracture.

The grandmother had two children. The elder, the patient's mother (now dead), had very marked blueness of the scleræ, was deaf, and is known to have had one fracture (toe). The younger (♂) showed none of the family peculiarities.

The patient's mother had four children. The eldest (♀), aged 40, shows no sign of the disease. The second (♂) died in infancy from an unknown cause, and so far as is known the disease did not appear in him. The third (♀), aged 36, has blue scleræ, is deaf and has had one fracture (rib). The patient herself is the youngest child.

The patient's eldest sister, who has been twice married, has two children, both boys, one by each husband. In the elder, aged 15, it has recently been noticed that his 'eyes are turning blue.' Neither is deaf and neither has had a fracture.

The second sister has had ten children, two of whom died in infancy. Of the survivors, the eldest and the youngest are girls aged 14 and 2½ years respectively, the others are boys ranging from 12 to 5 years of age. The eldest has blue scleræ, has once fractured a bone (clavicle), and though not deaf, has complained of noises in the head. The six boys all show the blue coloration of the scleræ except one, the youngest but one, aged 7 years. None of them are deaf and no fractures have occurred in them. The youngest has very marked blueness of the scleræ and has recently broken her leg by falling off a chair.

The patient herself has one child (♀) aged 5 years. This child has 'blue eyes' but does not appear to be deaf. She had an acute otitis media at the age of 2. She has never had a fracture. She walked at a normal age and appears healthy.

The writer has had the opportunity of seeing the following members of the patient's family:—

(1) The eldest sister who shows no sign of the disease.

(2) The second sister. In this case the scleræ are of a deep blue colour, and a very well-marked arcus senilis is present in each cornea. She is not so hard of hearing as her younger sister.

(3) The patient's daughter who has slightly blue scleræ.

(4) The eldest sister's 'blue eyed' son. The blue tint is very slight but definite. It is more marked close to the cornea, and gradually shades off towards the outer part of the eyeball.

(5) The two eldest of the younger sister's children. In both of them the blueness of the scleræ is very striking.

None of the children as yet shows the arcus senilis. All appear healthy and well grown. The genealogical table opposite shows these relationships.

GENEALOGICAL TABLE.

B = blue scleræ. D = deafness. F = fractures (number in brackets).

Discussion.

This case displays a number of the features which are now recognized as those of Lobstein's disease. Fragility of bone is not in itself pathognomonic, occurring in connexion with various other conditions, such as rickets, senile atrophy, etc. Apert[1] gives the following list of characteristics which, occurring in combination, constitute Lobstein's disease:—

(1) Fragility of the bones.

(2) Peculiar conformation and structure of the bones.

(3) Peculiar shape of the skull.

(4) Laxity of ligaments, leading to excessive mobility of the joints and in some cases to repeated dislocations.

(5) Blue coloration of the scleræ.

(6) Deafness.

(7) Abnormal electrical reaction of the muscles.

(8) Other miscellaneous abnormalities, more rarely seen: unusually fine hair, white patches in the nails, deficiency of the teeth in enamel. The subjects of Lobstein's disease have been stated to show a special liability to migraine and various vasomotor disturbances.

(9) The familial character of the disease.

Functional and structural abnormality of the bones.—The fragility of the bones may become manifest at any time after birth, sometimes not for a number of years. It expresses itself in a tendency to repeated fractures, often the result of very trivial violence, and often, therefore, subperiosteal and associated with but little displacement. On the other hand, if the fracturing force is more considerable, comminution is more apt to occur than in a normal bone. The fractures heal readily in the usual way. The long bones are slender, often curved, the cortex very thin. The bones are unduly transparent to the X-rays. The chemical composition appears to be normal. Lobstein believed that the medulla of the bones is primarily affected in these cases, and that the essential lesion is an expansion of the medullary cavity at the expense of the cortical part of the bone, as the result of the primary pathological change in the medulla.

Schuchardt[36] suggested that the cause of the condition is to be found not in an affection of the medulla but in a dysplasia of the periosteum. This view met with considerable opposition. Rebbeling[32] pointed out that resorption of callus by the periosteal cells, following a fracture, is more than usually rapid in these cases; and Dœring[13] argued that the cellular proliferation seen in the periosteum excluded any atrophy of the latter.

Looser[28], on the histological examination of cases of osteopsathyrosis, found evidence of deficient function on the part of the osteogenetic cells of both marrow and periosteum, and of increased osteoclastic activity. Looser's observations and conclusions received support from Schmorl[35], Fowler[16], Lovett and Nichols[29], Fuchs[20] and others. Some authors, however, maintain that the osteoclasts are not in excess of normal. It appears to be agreed that the outstanding histological feature is the relatively small amount of ground substance as compared with the number of osteoblasts present. The periosteum is thin, the marrow and epiphyseal cartilages normal.

Shape of skull.—The cranium appears flattened from above downwards and expanded in its other diameters (' crâne à rebord '). There is thus an abnormal prominence of the occipital and temporal regions. In the latter situation especially the bulging may be so marked that the upper part of the pinna is pushed outwards and folded upon the lower part. Arlabosse[2] records a case where the cranial abnormality was well marked.

Blue scleræ.—Spurway[38] seems to have been the first to draw attention to the fact that blue coloration of the scleræ is present in typical cases of Lobstein's disease. Eddowes[14], who also reported a case of blue scleræ, suggested that the disease represents an abnormality of the supporting tissues of the body. Buchanan[11] found on histological examination that the scleræ are abnormally thin, allowing the uveal pigment to show through. Bronson, on the other hand, found the scleræ to be of normal thickness, but deficient in calcium, and hence unduly transparent. Apart from the blue coloration of the scleræ, other ocular abnormalities appear to be fairly common. Peters[31] and others have noted the premature development of arcus senilis. Congenital defects such as cataract, coloboma, etc., have also been reported.

Deafness.—Van den Hoeve and de Kleyn[21] observed several cases, in some of which the deafness was the result of otosclerosis. It may be noted that Dighton[12] had previously published a case as one of nerve deafness. The type of deafness varies. In some of the published cases it has been of middle ear type, in others labyrinthine, while in some it has partaken of the characters of both, as in a case recorded by Friedberg[18]. In Dighton's case the deafness was labyrinthine. In van den Hoeve and de Kleyn's second case there was no proof of otosclerosis. Voorhoeve's[39] four cases had labyrinthine deafness. Of Ruttin's[34] cases, in three the deafness was labyrinthine origin, in three otosclerotic. Kompanejetz[25] reported three cases with labyrinthine deafness, with or without otosclerosis in addition. Bigler[9] described a family of which one member had otosclerosis, another labyrinthine disease. Apert[1] regards the deafness as due to abnormal thinness of the tympanic membrane and laxity of the ligaments attached to the ossicles.

Abnormal electrical reaction of the muscles.—This has been noted by several observers, including Larat and Bolton. The response to faradic stimulation is weak, and with the galvanic current there is a greatly diminished response and the rapidity of both contraction and relaxation is much below normal, so that the form of contraction resembles that characteristic of smooth muscle. In effect, there is an incomplete reaction of degeneration. All the muscles are alike involved, not only those attached to the affected bones.

Heredity.—Of the hereditary character of osteopsathyrosis there can be no doubt. Among the reported cases in which the hereditary factor is well marked, those of Spurway[38], in which four generations of one family were involved, and of Holcomb[23], in which five generations were affected, are especially noteworthy. As regards the exact mechanism concerned, the evidence is conflicting. Bauer and Stein[6] maintain that the deafness is associated with two recessive Mendelian factors, while other authors (e.g., Apert, Holcomb) have found evidence of a dominant factor. The question is further discussed by Aschner and Engelmann[3]. Individual cases of osteopsathyrosis display the distinctive features of the disease in varying combination: a given case may exhibit any or all of them. Blue scleræ, for instance, may be the only apparent abnormality (J. Bauer[5]). Apert maintains that in any given family the combination of symptoms remains constant, though some abnormalities may be less well developed than others. That the various characteristics may occur in different degrees of development is clear from the recorded cases. In those described by Voorhoeve[39], for instance, the blue coloration of the scleræ was much more marked in some than in others. Thus the deafness or the fragility of bone or any of the other features of the disease may be inconspicuous or absent in any individual case. Francke[17] expresses the opinion that the complete syndrome (blue scleræ, deafness, fragile bones) is found only in people whose parents have also shown it.

Ætiology and pathology.—The question has been much discussed, what relation (if any) Lobstein's disease bears to the condition known as congenital osteogenesis imperfecta. Despite the fact that many cases of each disease have been investigated, this problem has not yet been solved. It remains uncertain whether the two conditions represent, as many authors hold, two different aspects of the same abnormality; or if, as others assert, they are unrelated maladies bearing merely a superficial resemblance to one another.

Congenital osteogenesis imperfecta was first described by Vrolick in 1845. Its chief clinical characteristic is undue fragility of the bones. This may first manifest itself in intra-uterine life*, and results in multiple fractures.

* H. A. T. Fairbank (*Proc. R. Soc. Med.*, Lond., 1930, XXIII, 1263, Child. Sect. 77) is of opinion that both ante-natal and post-natal cases are of intra-uterine origin, the date of the first fracture depending on the severity of the affection in a given case.

The children are often stillborn, and if they survive continue to suffer from frequent fractures occurring as the result of trivial causes. The bones may be either short and thick or long and slender in form, and are very poorly calcified. Heredity is sometimes a marked factor. The majority (about 80 per cent.) of the recorded cases have been in the female sex. Associated with the fragility of the bones there may be other abnormalities, such as imperfect ossification of the cranial bones with non-closure of the sutures, ' crâne à rebord ' and blueness of the scleræ: Bentivoglio and others have reported cases in which muscular hypotonia, with histological changes in the muscles, has been present. Since the disease so often results in the child being stillborn, many opportunities for post-mortem examination have arisen, in contrast to Lobstein's disease, in which material for pathological examination has been chiefly obtained, so far, from osteotomy operations. The chief anatomical peculiarities found on autopsy are defective ossification of the bones and imperfect development of the teeth. Jeckeln[24] has recently published a detailed account of the histological appearances. He describes a disturbance of the normal process of ossification. Changes, according to him, are first apparent in the zone of cartilage-cell columns; they include deviations from the normal longitudinal arrangement of the cell columns and disturbance of the normal relationship between the size of the cells and the amount of intercellular material, the latter being considerably reduced. In the ossifying zone trabeculæ are laid down but remain chiefly cellular; very little ground-substance is produced and calcification takes place most irregularly, some trabeculæ staining normally with hæmatoxylin-eosin, others showing little or no evidence of calcification. There is, in fact, evidence that the function of the osteoblasts is imperfectly carried out. According to Jeckeln the number of osteoclasts present is not in excess of the normal.

As regards the tooth-germs Jeckeln describes enamel formation as proceeding normally. Abnormal conditions, however, obtain in the pulp. The odontoblasts in the early stages appear normal, but soon begin to show retrogressive changes, with the result that both the formation and calcification of the dentine are imperfect.

Although many authors maintain that the cause of osteogenesis imperfecta is deficient osteoblastic function, some have stated that it is to be found in abnormal activity of the osteoclasts. They point out that rapid healing of the fractures, with exuberant callus-formation, is usual. Harbitz, Buday and others claim to have shown that the osteoclasts are increased both in numbers and in functional activity, resulting in expansion of medullary cavity. Jeckeln's[24] case furnishes evidence against the view that the osteoclasts are responsible for the condition. Frontali[19] has reported a case where there was complete absence of compact substance in the tubular bones, while the cancellous substance was of fibrous structure and there was no formation of lamellæ or Haversian canals; in this case also, histological examination revealed very few osteoclasts, and the osteoblasts were few in number and abnormal in appearance.

Those who maintain that osteopsathyrosis and osteogenesis imperfecta are merely two aspects of the same condition base their contention upon the similarity of the structural changes in the bones and of the clinical features; and, in particular, upon the occurrence of both types in the same family, several examples of which have been reported. For instance, Tillaye (quoted by Sorrentino[37]) has described a family of five children all subjects of fragility of the bones, in whom the first fracture to be noted occurred at the ages of 29 years, 20 years, 2 months, 6 weeks, and 8 days respectively: Lovett and Nichols[29] have recorded the occurrence of osteopsathyrosis in the parent and osteogenesis imperfecta in the child. In this connexion, however, it should be borne in mind that a fracture in very early life may easily be overlooked. Blueness of the scleræ may occur in either disease. There would appear clinically to be no sharp line of demarcation between osteogenesis imperfecta and osteopsathyrosis; the distinction is to be found in the time of onset, in ante-natal life in the former, after birth in the latter. As regards the histological changes, Looser[28] found that those presented by his cases of osteopsathyrosis corresponded to those described in the published cases of osteogenesis imperfecta. Both showed evidence of deficient osteoblastic function, while the epiphyseal cartilage, preliminary calcification of cartilage and resorption of bone appeared normal. The relatively large numbers of cells present, and the rapid formation of callus which follows a fracture are similar in both diseases. Looser therefore made the suggestion that the essential unity of the two conditions should be recognized by giving to osteopsathyrosis the name of osteogenesis imperfecta tarda. Neither name can be regarded as satisfactory, since neither takes into account all the varied features of the disease. It is perhaps best, at the present time, to use the non-committal name of Lobstein's disease in referring to the condition, although Lobstein's own account of it was very incomplete.

Much discussion has taken place as to the essential nature and causation of these diseases. Hildebrand, in 1899, suggested that osteogenesis imperfecta is due to the injurious action of some toxin upon the osteoblasts. Biebl[8] amplified this hypothesis, the results of his work on the teeth leading him to suggest a toxæmia of pregnancy as the cause. Fahr[15] and others have postulated an endocrine origin. Changes have been described in the thymus, thyroid, pituitary, etc. Macciotta[30] suggests that the condition is due to an anomaly of cholesterin metabolism (reduction of the amount of cholesterin present in the blood) associated with changes in the suprarenal cortex. Kraus[26], on the other hand, brings evidence against the theory of an endocrine deficiency or dysfunction. Vitamin deficiency has also been held responsible. Stress has been laid on the anatomical resemblance between osteogenesis imperfecta and scurvy, but it now appears that in the former disease the marrow is at first unaffected, only later showing secondary changes. As regards Lobstein's disease, Axhausen[4] has expressed the opinion that the disease is akin to osteomalacia, and this view has been

supported by Recklinghausen[33]. Others have suggested disease of the spinal cord, others again syphilis as the cause.

It is clear that as regards osteopsathyrosis none of these hypotheses can stand against the weight of evidence that has accumulated to show that the disease arises by hereditary transmission. If we accept the view that osteogenesis imperfecta is merely the pre-natal form of osteopsathyrosis, it is necessary to find some explanation which will cover both diseases. The most important hypothesis at present put forward is that of an inherited anomaly of certain tissues of the body of which the cause, like that of other congenital defects, is unknown. This view has been expanded by various authors, especially by Hoffmann[22], more recently by K. H. Bauer[7]. Bauer bases his conclusions chiefly upon the pathological findings in one case, a seven months' fœtus (female) with osteogenesis imperfecta, and upon the clinical features of a case of osteopsathyrosis in a boy of eleven. Like Looser, Bauer regards the two diseases as identical. In the former case post-mortem examination revealed changes in the bones, teeth and connective tissues, together with excessive development of the lymphatic tissues (status lymphaticus), calcification of the intima of the arteries and the presence of eosinophil leucocytes in the lymphatic glands, thymus, pituitary and spleen. In his case of osteopsathyrosis Bauer also found enlarged tonsils and adenoids.

On this evidence Bauer concluded, in his first paper, that osteogenesis imperfecta is a disorder affecting the connective tissues as a whole, manifesting itself as a dysfunction of all matrix-forming cells. In his second paper he went further, and expressed the view that osteogenesis imperfecta and osteopsathyrosis are the result of an inherited constitutional anomaly (inferiority or deficiency) of the tissues derived from the mesoderm, or more precisely from the mesenchyme. His suggestion is that while all tissues of mesenchymal origin are involved, the more highly organized tissues (bone, cartilage, pulp of teeth) are chiefly affected. He failed to discover any changes in the muscles (striated and unstriated), the urinary or genital organs or the suprarenal cortex, whence he concluded that only the mesenchymal part of the primitive mesoderm is involved. Cell-formation is not necessarily deficient (as exemplified by a case reported by Buday, where osteoblasts were present in great numbers and were of normal structure), but the matrix-forming function is always impaired.

Later cases of osteogenesis imperfecta reported by Fahr[15] and by Kraus[26] failed to confirm Bauer's mesenchymal theory. Fahr, moreover, found evidence of excessive development of the thyroid and thymus (derived from the entoderm), pituitary and suprarenal medulla (derived from the ectoderm), but again only in one unconfirmed case.

Since the publication of Bauer's hypothesis, various observers have described changes in other tissues of mesodermal origin: such as the muscular

hypotonia and structural changes already alluded to (Bentivoglio and others), and excess of lymphocytes in the blood (Frontali, Macciotta and others). General œdema has been described in some of the recorded cases, and has been accounted for in terms of the mesenchymal deficiency hypothesis, by assuming that it is due to primary insufficiency of the vessel walls. Against this view it has been urged that œdema is a common symptom of children's ailments, especially those of the bones, and may in these cases also be merely symptomatic. Recent work has tended to cast doubt upon Bauer's hypothesis. Friedberg[18], for instance, holds that the evidence of changes in other mesodermal tissues (subcutaneous connective tissue, tendons, ligaments, the capsules and interstitial connective tissue of the internal organs, the blood and blood-vessels, lymphatics and glands, muscles and urogenital organs) is inconclusive, and points out that abnormalities have been found in tissues of other than mesodermal origin. Fahr, as already mentioned, describes changes in the endocrine glands derived both from the ectoderm and the entoderm. In the case of osteopsathyrosis reported by Blegvad and Haxthausen[10] there was zonular cataract as well as blue discoloration of the scleræ. In other reported cases the blue scleræ have been accompanied by delayed development of the teeth, cleft palate and syndactyly. Further, as already seen, the deafness may be due to a lesion of the labyrinth: the degeneration of the auditory nerve underlying this type of hereditary deafness cannot be reconciled with the mesodermal deficiency hypothesis. It would appear that in osteogenesis imperfecta, using the term in its widest sense, we are dealing not with a system-disease of the mesoderm or mesenchyme, but with a connected group of constitutional anomalies. Such a condition might be due either to a primary failure of development, or as Jeckeln[24] suggests, to interruption of the normal progress of development. This author, from the results of his observations on dentine formation in a case of congenital osteogenesis imperfecta, postulates a condition of progressive exhaustion of osteoblastic function, with intervals of remission. He suggests that this hypothesis would throw light upon the essential nature of osteopsathyrosis (osteogenesis imperfecta tarda).

General conclusions.

In the case of Lobstein's disease described above, the familial aspect is well marked, cases having occurred in four generations. The inheritance has been direct from mother to child, except in one instance, that of the patient's eldest sister's son, who has the blue scleræ and whose mother has shown no signs of the disease. The direct character of the inheritance, the number of members of the family showing the peculiarity and the constancy with which the disease has appeared in each generation would seem to point to a Mendelian dominant factor being concerned. The case of the boy just mentioned is difficult to reconcile with the others. There are four possibilities: (1) The father (now dead) might have belonged to a family in which the disease was present. This is denied; and the father himself, who was in

no way related to the mother, is said to have shown no sign of the disease. (2) The mother may later develop signs of the disease, the taint being as yet latent in her. (3) The factor concerned may not be a dominant one. (4) The case may not be a genuine one of Lobstein's disease.

In this family fragility of bone has been but little in evidence; fractures have been few. It is possible that in the case of the patient herself the scoliosis (see below) is caused by some defect of ossification of the vertebræ; or that it is due to muscular hypotonia, which again may be a manifestation of the disease. It may, however, be merely coincident.

Another point in connection with this family is the more marked incidence of the disease among female members. No fracture is known to have occurred in any of the males of the family, and the complete triad of symptoms (blue scleræ, deafness, fractures) has only appeared in the females.

As in many other of the recorded examples, the anomaly in the instance here reported appears to involve certain tissues of epiblastic origin (enamel, auditory nerve) as well as tissues derived from the mesoderm; the case thus according with the view that Bauer's hypothesis of mesenchymal deficiency is not a true explanation of Lobstein's disease.

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THE PLASMA PHOSPHATASE IN RICKETS AND SCURVY

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Robison[8] in 1923 first described an enzyme which was concerned with the calcification and the growth of bone. He pointed out that the deposition of calcium phosphate in growing bone and its non-deposition elsewhere had not up to that time been explained. In 1904, Pfaundler[3] had assumed a specific adsorption of calcium ions by the cartilage, with the consequent precipitation of insoluble salts. Later, Adler[1] pointed out that an aqueous solution containing the same amounts of calcium phosphate and carbonate as are present in serum would be saturated with respect to these salts which would tend to be precipitated from the solution. The failure of this to occur in serum was attributed by Pauli and Samec[2] to an increased solubility of calcium in the presence of the serum proteins, but the mechanism of specific adsorption of calcium from a solution such as is presented by blood had not been made clear, and the work of Robison has suggested a chemical rather than a physical basis for calcification.

Robison's hypothesis may be briefly stated as follows:—The osteoblasts and hypertrophic cartilage cells secrete an active enzyme, a phosphatase, which by hydrolyzing the phosphoric esters of the blood brings about a local increase in the concentration of the various inorganic phosphate ions. The solubility product of tertiary calcium phosphate is thereby exceeded and deposition of this salt occurs in the ossifying zone. This enzyme is present in considerable quantity in ossifying cartilage and to an equal extent in teeth. It is present in greatest amount in bone at the time when deposition of bone is most active, and is absent from cartilages which do not calcify, as, for example, tracheal cartilage.

Robison's hypothesis has received further confirmation from the results of his experiments on calcification in vitro[10]. He was able to demonstrate that a rachitic bone, split lengthwise and immersed in a solution of calcium glycerophosphate or calcium hexosemonophosphate, showed a deposition of calcium phosphate in the zones of preparatory calcification and hypertrophic cartilage cells, and in the periosteum.

Phosphatases are also found in the kidney, the intestinal mucosa and the blood plasma. The intestinal phosphatase is probably associated with the hydrolysis of the phosphoric esters in the food, while the renal phosphatase may be concerned with the appearance of inorganic phosphorus

in the urine. Although the relation of the renal and intestinal phosphatases to bone phosphatase is not clear, it seems likely that the bone phosphatase and the plasma phosphatase are identical.

Applying Robison's experimental work to clinical medicine, Kay and others[5, 6] have shown that in certain generalized diseases of bone the plasma phosphatase is markedly increased. The conditions which were first found to be associated with an increased plasma phosphatase were osteitis fibrosa, osteitis deformans, osteogenesis imperfecta, osteomalacia and rickets.

In view of these findings it was thought desirable to take a series of children with rickets, and to trace the course of the plasma phosphatase and its relation to the healing process. Later, the study was extended to other conditions such as scurvy and fractures.

Method.—The method used was that of Kay[4] adapted for use with small quantities of plasma.

Blood is collected from a finger prick in an oxalated tube of the type described by Martin and Lepper. 0·3 c.cm. of the centrifuged plasma, 1·5 c.cm. of N/100 hydrochloric acid, and 3 c.cm. of sodium β-glycerophosphate (0·15 per cent.) are mixed, and the carbon dioxide liberated from the plasma bicarbonate is extracted under reduced pressure with a water pump. 0·8 c.cm. of this solution is placed in each of 5 Monax test tubes graduated to 3 c.cm.; 0·5 c.cm. of 20 per cent. trichloracetic acid is added to tubes 1 and 2; a tiny drop of chloroform is placed in tubes 3, 4 and 5, and in tube 5 two drops of phenol red solution (0·02 per cent.). This tube (5) is titrated to pH 7·6 at room temperature by the addition of N/50 caustic soda from a micrometer burette (Trevan). An equal quantity of caustic soda is added to tubes 3 and 4 which may be expected to reach the same pH as tube 5. Tubes 3, 4 and 5 are corked and incubated at 37°C. for 48 hours, when the pH of tube 5 is again read; the change of pH in this tube is usually slight. This adjustment of the reaction is of considerable importance since the pH has a considerable influence on the velocity of hydrolysis (Martland[7], Robison[9]). 0·5 c.cm. trichloracetic acid is added to tubes 3 and 4, and the contents of tubes 1, 2, 3, and 4 made up to 3 c.cm. with distilled water. After standing for 10 minutes, these tubes are filtered and the phosphorus content of 2 c.cm. filtrate estimated by the Briggs modification of the Bell and Doisy method.

Results in normal infants and children.—In adults Kay[5] has found that the normal phosphatase varies from 0·1 to 0·21 units; he states that higher figures are common in infancy. We have found that the average phosphatase content in 14 infants under one year was 0·23 (range from 0·10 to 0·27). In the second year the average figure was 0·24, with a range of 0·11 to 0·33 units. The children in the first group were normal clinically and radiologically. All cases of the second group were normal radiologically, and as three had phosphatase values in the neighbourhood of 0·3, it is probable that high values up to 0·3 units must be considered to be within the normal range. The average plasma phosphatase of a series of seven normal children, whose ages varied from six to twelve years, was 0·17, with a range of 0·12 to 0·2 units.

Plasma phosphatase in rickets.—In all the cases one or more clinical signs of active rickets were present, such as epiphyseal enlargement, beading of the ribs, flabby muscles, delayed closure of the fontanelle, etc. Radiographically,

they all showed decalcification, enlargement of the epiphyses and irregularity of the epiphyseal line. The serum calcium and plasma phosphorus and phosphatase were estimated when each child was first seen in the active stage and at intervals while healing was in progress until this was complete. The progress of healing was checked both clinically and radiographically.

In a series of ten cases of uncomplicated rickets the calcium and phosphorus were both reduced to a greater or lesser degree; in two cases the calcium alone was lowered. The phosphatase in these cases averaged 0·76 units with a range of 0·4 to 1·4. In one case of early rickets the figure was only 0·3 units.

Two or three weeks after the commencement of treatment the calcium and phosphorus had risen to normal and maintained this level subsequently. The decline in the phosphatase on the other hand was much more gradual, and while the calcium and the phosphorus were normal soon after healing had begun, the phosphatase did not fall to normal until the healing process appeared complete.

These findings are illustrated by the following case:—

C. C., female, admitted on January 20th, 1931. She had been fed since one month old on boiled milk and barley water. Orange juice had been given regularly but no additional fat-soluble vitamins. When first seen at 5 months, she was pale and much underweight for her age even allowing for the fact that she had been born prematurely and that at birth her weight was 5½ lb. On admission, her weight was found to be 8 lb. There was marked beading of the ribs and enlargement of the epiphyses, but there was no clinical evidence to lead one to suspect such fractures of the long bones as were revealed by the radiograms. The liver was slightly enlarged and the blood count on January 29th, showed a secondary anæmia.

Treatment and progress.—The infant was fed on a humanized dried milk and a preparation of Vitamin D of which an amount equivalent to 2 mgrm. irradiated ergosterol was given twice daily from January 23rd to February 17th when, in view of the good progress in healing, the dose was reduced to 1 mgrm. twice daily. This dosage was continued until the child was discharged (see Table 1).

TABLE 1.

Analyses in a case (C.C.) with active rickets.

Age mths.	Date	Calcium mgrm.	Phosphorus mgrm.	Phosphatase units	Radiological appearances
5	26-1-31	6·2	2·0	0·57	Acute rickets *i.e.* epiphyseal cupping and enlargement, decalcification. Green stick fractures of one ulna, tibia and fibula.
	6-2-31	10·1	3·6	0·47	Healing commencing; calcification proceeding at bone ends; callus around sites of fractures.
	17-3-31		3·6	0·44	Good progress in healing, sites of fractures scarcely discernible. Epiphyseal cupping very slight.
8	23-4-31	10·4	4·5	0·24	Rickets healed.

Plasma phosphatase in scurvy.—Six cases of scurvy were examined. In three of these the diagnosis was based on the history of scorbutic diet, the presence of spongy gums and petechial hæmorrhages on the tongue or palate, the demonstration of red blood cells in the urine and the characteristic radiological appearance of the bones. The other three cases had sub-

FIG. 1. V.C. 28-9-31. Acute scurvy. Plasma phosphatase 0·15 units (v. Table 2).

periosteal hæmorrhages. In five of these cases seen in the acute stage, little or no alteration in the blood calcium and phosphorus was found, but the phosphatase in all the cases gave low figures, so that the average figure was 0·14 units as compared with the normal average of 0·23 at this age. The first three cases of scurvy examined had no subperiosteal hæmorrhages

and no further investigations were made. It is unfortunate in the light of later events that these were omitted as subsequent analyses in the second three cases (those with subperiosteal hæmorrhages) showed the phosphatase to be raised coincident with the calcification of the extravasated blood. Whether this increase of the enzyme is only associated with the calcifying

FIG. 2. V.C. 16-10-31. Scurvy : calcified areas surrounding femora. Plasma phosphatase 0·52 units (v. Table 2).

blood clot, and is absent in cases of healing scurvy without such hæmorrhages is uncertain, but it is hoped that further investigation will clear up this point.

Table 2 shows the changes in the phosphatase values and the correlated radiological appearances in one of these cases.

TABLE 2.

ANALYSES IN A CASE OF SCURVY (V.C.) WITH SUBPERIOSTEAL HÆMORRHAGES.

Age mths.	Date.	Calcium mgrm.	Phosphorus mgrm.	Phosphatase units	Radiological appearances
9	29-9-31	10·0	3·4	0·15	Typical acute scurvy both clinically and radiologically. Large tender swelling above right knee on admission; similar swelling appeared above left knee a few days later. Hæmorrhage not visible in radiogram at this date.
	13-10-31	9·3	4·4	0·52	Large calcifying hæmorrhages ensheathing both femora.
	26-10-31	—	5·7	0·4	Hæmorrhages more sharply defined.
	9-11-31	—	—	0·43	Lamination visible.
	24-11-31	—	—	0·41	Little difference noted in the size of the calcifying areas.
13	25-1-32	—	—	0·3	Opaque areas gradually diminishing.
15	4-4-32	—	—	0·252	Bone contour almost normal.

Plasma phosphatase in fractures.—Additional evidence of the role played by phosphatase in calcification and ossification has been obtained in six cases of fractures. Immediately after the injury the phosphatase was normal, but about 10 days later there was a considerable rise. This increase was

FIG. 3. W.C. 26-10-31. Fractured femur.
Plasma phosphatase 0·17 units (v. Table 3).

maintained for some weeks, the elevation of the phosphatase corresponding to the amount of callus laid down and the length of time elapsing before healing was complete.

FIG. 4. W.C. 29-11-31. Fractured femur, lateral and antero-posterior views. Plasma phosphatase 0·32 units (v. Table 3).

Table 3 illustrates these findings in one of these six cases of fracture.

TABLE 3.

ANALYSES IN A CASE OF FRACTURED FEMUR (OCCURRING OCT. 26TH 1931) IN A CHILD (W.C.) OF SIX YEARS.

Date	Calcium mgrm.	Phosphorus mgrm.	Phosphatase units	Radiological appearances
31-10-31	11·4	—	0·17	Oblique fracture mid shaft of femur. No callus visible.
6-11-31	—	3·5	0·34	Considerable amount of callus present.
29-11-31	—	—	0·32	Increased callus in skiagrams.
19-12-31	—	—	0·30	Little change in skiagram.
23-1-32	—	—	0·30	Still little difference.
23-2-32	—	—	0·26	Bone resuming normal contour and structure.
18-4-32	—	—	0·23	Normal; no trace of fracture.

Discussion.

It will be seen that the chemical changes in rickets and scurvy are to some extent contrasting, as might be expected from the other pathological findings in these conditions. In rickets, there is excessive proliferation of cartilage cells, increased vascularity, and the formation of a wide zone of osteoid tissue. The high phosphatase found in rickets is probably derived from these hypertrophic cartilage cells and osteoblasts which Robison has shown to be the source of the enzyme, and its presence in increased quantity supplies one of the factors essential for ossification.

In scurvy, on the other hand, the picture is one of cessation of growth and ossification is in abeyance. The cartilage cells are disorganized and are fewer in number and smaller in size than normal. Hence, in the acute stage, there is neither the source nor the need for the production of phosphatase. This holds good also in cases with subperiosteal hæmorrhage before calcification begins. With the administration of antiscorbutic vitamin growth begins again and calcification of any hæmorrhage present proceeds; the cartilage cells become active and the plasma phosphatase rises corresponding to a probable increase in the secretion of phosphatase in the bone. The findings in cases of fractures agree with these conclusions.

Conclusions.

1. The average normal plasma phosphatase in infants under one year was found to be 0·23 (range 0·10 to 0·27). In the second year the figures were slightly higher, average 0·24 (range 0·11 to 0·33), while the phosphatase content in older children up to 12 years of age averaged 0·17 (range 0·12 to 0·2).

2. The plasma phosphatase is increased in active rickets, the degree of elevation corresponding to the severity of the disease. The average phosphatase in nine cases of uncomplicated rickets was 0·75, with a range of 0·3 to 1·4. Whereas the blood calcium and phosphorus rapidly returned to normal with treatment, the decline in the phosphatase was much more gradual, and normal values were not regained until the healing process was complete.

3. The phosphatase was found to give low normal figures in the acute stage of scurvy whether subperiosteal hæmorrhages were present or not. A rise of the phosphatase appeared coincident with the onset of calcification of the hæmorrhages and this fell again with the absorption of these calcified areas.

4. The plasma phosphatase was normal in cases of fracture immediately after the injury, but rose at the same time as the callus appeared and fell to normal when the bone was completely healed.

The above investigations were carried out in the Mond Research Laboratory, and we wish to thank Dr. Eric Pritchard, the Medical Director, and the Staff of the Infants' Hospital, for the facilities given for this work, and also those elsewhere who have so kindly allowed us their cases for investigation.

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ACUTE OTITIS MEDIA IN INFANCY

BY

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Anatomy.—The tympanic membrane is the same size in the new-born as in the adult. It lies almost horizontal in the plane of the base of the skull, so that its lateral border is almost in the same plane as the superior wall of the meatus. Thus the postero-superior quadrant, the region in which bulging is usually detected, is very near the surface and next the inner limit of the superior wall of the meatus.

The meatus is cartilaginous, and runs upwards from its attachments to the tympanic ring, so that to straighten the meatus and enable a view of the tympanic membrane to be obtained, the lobule must be pulled downwards.

For examining the membrane and deep reaches of the meatus, the use of an electric otoscope[1], with a small speculum, is essential.

The mastoid process developes only towards the end of infancy. The aditus and antrum are present at birth. The latter lies above and somewhat behind the tympanic ring.

I have frequently operated upon infants of six months of age for mastoiditis, and found an extensively pneumatized mastoid process.

Classification.—Acute otitis media in infancy may be described under various headings:—

1. Otitis media neonatorum.
2. Agonal otitis of infancy.
3. Otitis media of infancy.

Of these groups the first two are latent or clinically obscure in type.

(1) Otitis media neonatorum.

This is not an uncommon disease of the new-born. I have operated on a mastoid abscess in an infant of 5 weeks of age, in which the ear disease must have been present for at least three weeks. Deaths in infants soon after birth from meningitis are commonly due to an acute otitis media that has escaped detection during life (cf. Dodds[2]).

In the new-born, the tympanum is filled with gelatinous material. This acts as a good culture medium for the bacteria introduced soon after respiration and deglutition occur, by a retrograde extension along the Eustachian tube. This latter first functions after birth. The ear may become infected during labour. The initial deglutition and aspiration inoculates the gelatinous material in the tympanum. The embryonic connective tissue in the middle ear cleft, usually disappears some time after birth, but may do so before birth. Not only bacteria, but liquor amnii, vernix caseosa, fluid, meconium or pus have been found in the tympanum of the new-born. The ear is situated at some depth from the surface, so that inflammation may proceed in it for some time without becoming manifest. Hence any low grade or sub-acute infection will certainly escape detection, in the absence of otorrhœa.

Otitis media may be present within the first hours of birth. The lesion may be suspected and detected solely by the fact that the infant has a very high temperature, the origin of which is obscure. In the routine examination for the cause, the tympanic membrane is examined. It is found to be bulging, though the infection may be slight, and most of the tympanic and meatal landmarks are plainly identifiable.

In an infant only 24 hours old, admitted under the care of Dr. Sidney Owen, with a temperature of 103°, the tympanic membrane was bulging, but pale, with some injection. Myringotomy revealed pus, and the temperature subsided. This was an example of pyrexia neonatorum.

Another common way for the otitis to become overt in the new-born is the detection of a blood-stained discharge from the meatus, followed later by pus. On the other hand, nothing may be noticed until a lump forms behind the ear, i.e., a mastoiditis has occurred. Any of the syndromes of otitis media as it occurs in infants may occur in the new-born.

In 800 consecutive post-mortem examinations on infants up to 28 days old, no case of ear disease was recorded (Cruickshank[4]), but the examination of the ear must have been omitted. According to Malherbe[5], in infants, pus will frequently be found in the tympanum and antrum. The suggestion has been made that some prophylactic measures be instituted against the onset of these suppurative aural lesions in the new-born. Such a measure is the routine instillation of two to five drops of argyrol (1 per cent.) into the nose of the infant night and morning for a few days after birth, the head being dependent, so that the drops gravitate to the post-nasal region.

(2) Agonal otitis in infants.

Rizzi[6] states that in all autopsies on infants up to two years of age one-quarter showed the presence of otitis media, and of these, two-thirds showed a bilateral otitis media. In most cases a mixed infection was found, and in only a few instances was a pure culture (pneumococcal) obtained. The ear lesion was frequently found in cases succumbing to acute pulmonary conditions. The otitis was latent, symptomless, and usually only detected

at autopsy. In some cases gastro-enteritis was present, but out of 200 cases on which these figures were based, in no instance was death ascribed as due to it. The tissues of the middle ear cleft undergo rapid post-mortem changes, with the result that the cavities become filled with purulent fluid (Alexander[7]). Hence the purulent collections in the middle ear found at autopsy, may be post-mortem in origin.

Changes in the tympanic membrane, as Maybaum[9] has emphasized, are frequently observed in the terminal stages of many fatal diseases.

Otitis media, gastro-enteritis and respiratory disease.—This association is observed in children's hospitals usually by the physician, as the gastro-enteritis or the respiratory disease is the condition which brings the case under observation. These patients never appear before the otologist initially as ear cases, and there is room for close collaboration between the physician and the otologist, in the elucidation of the problems in connexion with these conditions, whose association is proved by autopsy records.

In 300 post-mortem examinations, in cases dying of malnutrition, Odenael[9] found that 80 per cent. had pus in the mastoid antrum, and 50 per cent. had pus in the maxillary antrum. The mastoid condition was considered to be primary, and not secondary to the malnutrition. According to this author, if vitamin A is withheld from an animal's diet, pus is found in the nasal sinuses, and although there can be little doubt that the purulent aural lesion may be an agonal infection, it may in some cases be the cause of the gastro-enteritis. With the predominance of this latter disease, the ear condition may be overlooked, as it is usually latent, that is to say, the ear is not discharging, and the tympanic membrane is apparently but little different from normal on inspection; yet exploration of the tympanum or mastoid antrum may reveal purulent lesions.

The relation of the ear condition to the gastro-intestinal disturbance is one on which many diverse views are expressed. The acute suppurative aural condition may affect the gastro-intestinal track with bad effect on both the ear and the intestinal condition (Bottacin[10]), so that a fatal termination is frequent. On the other hand, it is stated by Matison[11], and Girard[12], that the ear is the primary condition. The gastro-enteritis may take a favourable turn after antral drainage has been established. In my opinion, myringotomy is not sufficient.

In 70 consecutive post-mortem examinations on infants dying of diarrhœa and vomiting, Alden and Lyman[13] found that all had suppuration in the middle ear.

Otologist and pediatrist working together observed 39 cases of gastro-enteritis (Maybaum[8]). In the majority of cases, the ears were normal. Of these cases, 22 died, and in 16 the tympanic membrane was normal; in three cases the membrane showed marked changes with pus in the tympanum and antrum, in three other cases the membrane showed slight changes. No

bone necrosis was observed in any of the autopsy cases. Of the 17 cases that recovered, the normal membrane was found in five, minor changes in five, and marked changes in five. It was confirmed that the accumulation or infection in the mastoid is an ante-mortem process. The conclusion arrived at was that the intestinal toxæmia was not of otitic origin. (Maybaum[8], Wishart[14], Druss[15]).

The lesion found in these cases differs from the ordinary suppurative otitis by being completely devoid of all those signs usually associated with a suppurative lesion. The picture is a pale one. The lesion appears indolent. There are no inflammatory signs present, nor is there any inflammatory reaction in the surrounding parts. The condition simulates a cold abscess. There is no injection, no pain, and there is no swelling if we except a slight bulge in the membrane. Similarly there is no temperature or local heat, and no apparent loss of function: yet the lesion is suppurative.

The indolence of the lesion lends much support to the hypothesis that the whole condition is a terminal or agonal one occurring in a moribund patient, whose power of resistance is so enfeebled as to prevent any reaction occurring. The pus may result from purulent agonal or post-mortem decomposition (see agonal otitis). The patient is so debilitated that no inflammatory reaction occurs. Whether the ear lesion is post or propter hoc in relation to the intestinal condition, is still undecided.

The fact that pus has also been found in the nasal sinuses, is in support of the hypothesis that the disease is an agonal one. Moreover, in cases of frank mastoiditis or otitis, while occasional vomiting may occur, persistent vomiting does not occur, unless meningitis or some other intra-cranial complication is present. Diarrhœa never occurs even when a fatal issue results.

It seems, therefore, much against the hypothesis that the gastro-enteritis is secondary to the otitis or mastoiditis, that the aural conditions, when primary, should be conspicuously free from diarrhœa and recurrent vomiting, and also show all the criteria of inflammation, pain, pyrexia, swelling and injection, which are absent in the otitis associated with gastro-enteritis.

In view of these difficulties it seems to be a good rule in practice that in a case of gastro-enteritis in an infant, the ears should receive expert examination with a view to detecting an infective focus in the tympanum or antrum.

In a recent case of diarrhœa and vomiting in an infant the tympanic membrane could only be described as not normal. It was incised, and under local anæsthesia, the mastoid antrum rapidly opened. Pus was found therein. The gastro-intestinal symptoms rapidly abated, but recurred with drainage of the other antrum, convalescence was uninterrupted.

In the case of a weakly infant with diarrhœa and vomiting for nine days, under the care of Dr. D. Winnicott, the infant was noticed to be constantly putting his hand up to the right ear. The tympanic membrane was white, devoid of any signs of inflammation, but somewhat bulging. Myringotomy revealed pure pus. The tympanum and its inner wall were pale, and shewed no signs of inflammation, giving

the impression of pure pus having been poured into a normal tympanic cavity. The vomiting thereupon ceased and the child took the first feed for days. The symptoms then recurred and the other ear was incised. The case, however, terminated fatally. At autopsy the mastoid antrum on each side was full of pus. There was no bony involvement. Mere myringotomy will not drain the condition, as there is a narrow isthmus formed by the aditus which separates off the antrum. The latter must be drained by an antrotomy.

Otoscopic appearances.—In these cases, these are very little removed from the normal. The expert cannot say more, as a rule, than that the membrane is not absolutely normal. There may be slight bulging in the postero-superior quandrant, or the entire drum may be bulging with the umbo forming a dimple in the centre. As the plane of the membrane is a continuation of the superior wall of the meatus, the superior bulge is very near the advancing edge of the speculum. It is far more superficial than is at first realized. The membrane shows no injection.

Treatment.—Prophylaxis should be enjoined in all cases of gastro-enteritis. Argyrol should be instilled into the nostrils daily as described above. In frank cases of gastro-enteritis, the ears should be closely inspected and if myringotomy reveals pus, the antrum drained. This may be done under a local anæsthetic, such as 1 per cent. novocain, and should not take long to perform, as the antrum is separated from the surface by a thin plate of cartilage. As the facial nerve is emerging from the stylo-mastoid foramen in infants, it lies very superficially just lateral to the postero-inferior angle of the tympanic membrane. It is thus in grave danger of injury if the incision behind the ear extends down too low or too far forward.

Some advise myringotomy alone, and Alden and Lyman[13] have recorded cessation of symptoms following this procedure.

(3) Otitis media purulenta of infancy.

In frank otitis media, the presenting symptom is usually one of the following:—(a) Pyrexia of unknown origin; (b) obvious earache; (c) a sanguineous or purulent discharge from the ear; or (d) symptoms suggestive of meningitis (meningism), or convulsions.

(a) **Pyrexia of obscure origin.**—In the new-born, as during infancy, a high temperature may be the sign of an acute otitis media, hence in all cases of ' pyrexia of obscure origin ' in the new born or during infancy, it is essential to examine the tympanic membranes thoroughly. With the onset of otorrhœa from rupture of the tympanic membrane or from myringotomy, the temperature falls to normal. The clinical fact must be borne in mind that a high temperature such as 103°, 104° or even 105°, may be produced by an otherwise symptomless acute otitis media.

The changes visible in the tympanic membrane may appear to be slight and out of proportion to the high temperature. The tympanic membrane may be obviously bulging, like a balloon tyre, the umbo being the indrawn central depression. The colour may be pale, or injected, but the normal

membranal landmarks, such as the handle of the malleus are easily visible and there is no injection present to speak of on the membrane, or on the meatal wall adjoining the membrane. Yet the onset of otorrhœa within 24 hours, with a fall of temperature, may settle the origin of the pyrexia.

In infants, it is possible for pus to be present in the tympanum, yet the tympanic membrane remain pale, free from injection, and not necessarily bulging. Hence it is that Alexander[16] advised prompt myringotomy, in all cases of earache with a temperature above 100°, on the ground that such a temperature indicates a suppurative lesion. Often the temperature alone is the guide whether to withhold myringotomy or perform it. Alexander further advises, that if a child has earache, and it can be elicited that at any time subsequent to the onset of the earache, the temperature was over 100°, then myringotomy is indicated, even if the temperature is only 99° when the child first attends.

With this view I am completely in accord, and have practised it at the children's hospital for some time. When it is remembered that acute otitis media in infants is a very common ailment in London hospital practice, the value of this dictum is obvious. The temperature is, as mentioned, the chief guide as to active treatment. Even a bulging tympanic membrane is not necessarily an indication for myringotomy, in spite of the earache being severe.

I have seen an infant with severe earache, which had been present for 48 hours, and had interfered with sleep. The tympanic membrane was bulging considerably, but was pale, and free from vascular injection. There was mastoid tenderness. The temperature was 99°, and had never been above that level. In view of this, myringotomy was withheld, and the ear condition healed up without perforation.

(b) **Earache.**—In infancy, a child may have a frank otitis media, yet be free from any symptoms indicating the presence of earache. It is, however, easy to overlook earache, with the result that the cause of the child's obvious pain is only rendered too apparent by the subsequent detection of bleeding or discharge from the ear. Certain points suggest the presence of earache. The presence of meningism is one, with nuchal rigidity or convulsions. Pulling the ear, and putting the hand constantly to the ears, are often the only symptoms to suggest earache. Constant crying with the above pointers, indicates the presence of earache, whether intrinsic (of true aural origin) or extrinsic (referred) origin. Banging the ear, resisting the attendant's attempt to reach the ear, may indicate which ear is the seat of the trouble. At the same time, the infant may move or roll the head from side to side with a regular pendulum movement, crying and restless all the time, until it falls into a fretful slumber. Attempts to palpate the mastoid, result in the infant throwing the head back towards the tender ear, and even give rise to a rigid neck.

(c) **Otorrhœa.**—The usual sequence in cases of acute otitis media is for the parent to observe a blood-stained ear discharge which soon becomes purulent. This may be the first and only symptom of the otitis.

The tympanic membrane is very resistent to the penetration of pus through it, and purulent secretions may drain down the Eustachian tube into the pharynx. This may only occur, if the infection is a relatively mild one. If, however, it is severe, pus does penetrate the membrane or extend to the antrum. The latter is superficial in infancy, being separated from the surface by a thin plate of cartilage, or patent persisting petro-squamosal suture. Pus may thus easily extend outside the confines of the antrum through the thin plate of cartilage or the suture, and produce an inflammatory swelling behind the ear.

(d) **Meningism.**—This is a syndrome that is peculiarly apt to occur in infants in the initial stages of an acute otitis media. As its name implies the condition simulates meningitis. Earache may be manifest or apparently absent. The infant is feverish, and throws the head back, with the result that nuchal rigidity becomes evident. Vomiting may occur, and restlessness. The child may be ill and have convulsions.

On examination of the tympanic membrane, it is found to be inflamed and/or bulging. With the rupture of the membrane and the discharge of the pus, or as a result of a myringotomy, the cerebral symptoms rapidly abate, following the liberation of the pent-up inflammatory products in the tympanum.

The cerebral symptomatology suggests a meningitis, but in meningism, the child sleeps, there is still pulsation in the fontanelle, and both the temperature and the pulse are raised. The condition only occurs in the commencing stages of an acute otitis.

In an established case of meningitis, the temperature is raised but the pulse is not proportionately so. The child is sleepless, restless, delirious, and may exhibit facial twitchings or grinding of the teeth. There is no pulsation in the anterior fontanelle, which is hard and distended. Kernig's sign and nuchal rigidity may be demonstrated. Lumbar puncture will settle the diagnosis, and should be performed where these symptoms are present. In meningism, if a lumbar puncture is performed, the fluid is normal, but under increased tension.

Cerebral symptoms occurring in a case of acute otitis, of some standing (after the membrane has perforated), are never due to meningism, but always due to meningitis.

Meningism never occurs in a chronic otitis media. Any such symptoms are due to meningitis. Thus mastoidism and meningism have this in common, that both occur only in the initial stage of the acute otitis before the membrane has been perforated by the suppuration, all the symptoms subsiding with this onflow of pus. Any symptoms persisting after this stage are due to mastoiditis or meningitis respectively.

Physical signs.—The physical signs of an otitis, in addition to the anomolous tympanic membranal changes mentioned above, may be an injected inflamed membrane, the redness extending on to the meatal wall

around. The congestion may be such as to obliterate the landmarks and to make it impossible to delimit the margins of the membrane. If the Siegle's attachment to the speculum is used, and aspiration practised, the suction will cause the membrane to move and so define its limits.

In an otitis media, there is never any swelling behind the ear, nor is there any sagging of the posterior superior meatal wall. Both these latter signs, when present in association with acute otitis, indicate the presence of a mastoiditis. As mentioned above, there is no true mastoid developed till after the sixth month, but by mastoiditis, before this age, is meant the extension of suppuration outside the confines of the mastoid antrum.

It must not be forgotten that the tympanic membrane may be white, without any injection, yet pus is deep to it. If there is earache and a temperature above 100°, the lesion is suppurative, even if the tympanic membrane displays this apparent absence of active inflammation. The membrane is never absolutely normal. It may be moist, bulging in one quadrant or the entire part; and the light reflex is always absent, the surface having lost its characteristic normal sheen.

Tenderness may be present in the initial stages of the otitis. This is indicated by the obvious distress produced by palpating behind the mastoid process. If the tympanic membrane is bulging and unruptured, the tenderness must be assumed to be due to the otitis, uncomplicated. If, however, there is no bulging and the membrane is perforated, and the discharge is free, any tenderness means a mastoiditis. This early tenderness, which is always an initial tenderness, disappearing as the discharge appears, is termed by Alexander[16], 'mastoidism.' The aditus, antrum and tympanum all form part and parcel of one cavity, and they may all be involved in the inflammation. Hence tenderness over the mastoid is only to be expected in the early stage of the disease.

Exfoliative otorrhœa.—There is a common fallacy to which attention must be drawn. The fact that the ear is stated to be discharging is no evidence that there is a purulent discharge, or that the membrane has perforated. Cleaning the meatus, by syringing and mopping with cotton wool wipes, will show that in a number of cases the tympanic membrane is still bulging, red and unperforated. What has happened is that the inflammatory products in the tympanum have produced an exfoliation or desquamation of the outer layer of the tympanic membrane, which is cast off into the meatus as a white debris, and appears as a discharge. Such a membrane requires myringotomy.

Cryptic otitis.—Where otitis media occurs in association with another disease, e.g., pneumonia, it not uncommonly happens that the ear inflammation is not revealed until a discharge from the meatus becomes overt. This cryptic otitis is frequent in attacks of the acute specific fevers. Hence in all instances of disease in which ear complications are prone to occur, should have the ears examined regularly.

Treatment.

Myringotomy is indicated in the presence of: (1) mastoidism; (2) meningism; (3) pyrexia above 100°, with earache; (4) a bulging membrane, in the presence of active inflammation of the tympanic membrane, or in the absence of the latter, in the presence of a high temperature.

During the painful period, glycerine and carbolic drops are to be advised, to be replaced as soon as the pain has subsided, by spirit drops. The ear should be regularly syringed with boric lotion, to keep it free of discharge. The infant should wear a cap over both ears, to keep them at an even temperature. Anodynes are to be given by mouth for the relief of pain and to ensure a good sleep. The case should be observed from day to day. Any severe and obvious naso-pharyngeal condition may require attention, e.g., tonsils and adenoids, if the ear condition tends to show no signs of resolution by the end of, say, six weeks. The usual rule is ' two to three days of pain, followed by two to three weeks of discharge.'

In those illnesses in which ear complications are known to occur with frequency, prophylactic measures are to be employed as already described.

Conclusions.

In dealing with the subject of acute otitis media in infancy in the preceding pages certain conclusions have been reached which are of sufficient practical importance to warrant their being summarized here for the sake of emphasis.

1. In an infant the tympanic membrane may remain of apparently normal colour, and yet have pus deep to it.

2. A temperature of over 100°, with an unruptured tympanic membrane, during an attack of acute otitis media, even though such a figure has been reached only once during the illness, indicates the presence of a suppurative lesion, demanding myringotomy without delay. Even if the patient is not seen until a late stage of the attack when only a mild degree of fever (99°) is present, the same conclusions should be drawn if there is a clear history of an earlier temperature of over 100°.

3. The presence of high fever in an infant, even in the newly born, should lead to a suspicion of acute otitis media calling for a careful examination of the ears.

4. In cases of infantile gastro-enteritis the ears should be kept under the observation of the otologist. If myringotomy reveals pus, the antrum should be drained.

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THE INFLUENCE OF ACIDOSIS ON CARBOHYDRATE METABOLISM

BY

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In 1922 it was demonstrated by Kaguera[1] that dogs given a high-fat diet over a certain period of time, showed an abnormal rise in the blood sugar after a glucose meal; and Southwood[2] in 1923 reported similar results in men who had been given a carbohydrate-free diet for 36 hours previous to the test. Numerous other investigators have confirmed these results, and how striking this hyperglycæmia can be has been demonstrated by me in a previous paper[3]. This reduction in sugar tolerance occurs not only with a carbohydrate-free diet, but also if the subject is deprived of all food; and Severinghaus[4] has found that after fasting for 48 hours the ingestion of glucose resulted in a blood-sugar reaction resembling that obtained in a mild case of diabetes mellitus.

The chemical changes in the blood which accompany a low carbohydrate diet are in some respects similar to those occurring in starvation, and consist of a non-gaseous acidosis, a diminished alkaline reserve and a ketosis. Some workers have considered that it is the change in acid-base equilibrium which is responsible for the modification in glucose metabolism. Henderson[5] has pointed out the intimate relationship between acid-base equilibrium and glucose metabolism, and Field and Newburgh[6] considered that an increased H-ion concentration had a depressing effect on the metabolism of sugar. Langfeldt[7], by administering acid either orally or intravenously, increased the H-ion concentration of the blood and produced an increased glycogenolysis.

Other hypotheses, however, have been brought forward to explain the change. Du Vigneaud and Karr[8] and Lennox[9], who reported results similar

* This work was done during the tenure of a McCunn Medical Research Scholarship.

to those of Severinghaus[4], suggested that the lack of carbohydrate was the important factor in producing the disturbance of glucose metabolism which occurred with the change in diet. It has been shown by MacLean and De Wesselow[10] that a second dose of glucose given as the blood sugar was falling after the rise due to a first, produced no secondary rise in the blood-sugar curve. They explained this by suggesting that the glycogenic function is stimulated by the hyperglycæmia produced by the first dose of glucose, and thus a second rise in blood sugar is prevented. Lennox[9], therefore, considered it possible that the lack of carbohydrate had deprived the sugar-disposing mechanism of the stimulation it required, and he was inclined to believe that this factor was of more importance than the disturbance in acid-base equilibrium.

There seem, therefore, to be three views regarding the disturbance of carbohydrate metabolism in ketosis: (1) That it is due to acidosis per se; (2) that it is due to the action of excess of ketone bodies; or (3) to a diminution in the stores of carbohydrate in the body. If it is due to acidosis pure and simple, the alteration in the pH of the blood by ammonium chloride should produce the same disturbance as ketosis; but if it is due to the action of ketosis, or merely to carbohydrate starvation, the metabolic disturbance of carbohydrate metabolism should differ from that produced by the drug.

Present investigations.—The investigations described in this paper were designed to throw some further light on this problem. Ammonium chloride, when administered to the normal individual in sufficient quantities, produces a marked disturbance in the acid-base equilibrium, shown by a non-gaseous acidosis and a reduced alkaline reserve, resembling the changes resulting from ingestion of a high-fat low-carbohydrate diet. Haldane[11] by ingesting large quantities of ammonium chloride caused a profound disturbance of his carbohydrate metabolism manifested by a marked reduction of his glucose tolerance. Lennox[9] found that a subject with a diminished alkaline reserve (CO_2 44 vol. per cent.) induced by the daily administration of 20 grm. of ammonium chloride for a period of 29 days, showed a curve lower than normal; whereas after a 17 days' fast the blood-sugar curve was diabetic in type though the acidosis was much less than when receiving ammonium chloride. In view of these results it was decided to test whether the metabolic disturbance brought about by ' diet acidosis ' differed in any way from that following ' drug acidosis.'

Glucose tolerance during high fat diet.—Eight children, convalescent from chorea or rheumatism (except Case 5 who had been treated for tapeworm) were the subjects of the tests. Their sugar tolerance on ordinary diet was estimated and the results, with those obtained on the special diet, are recorded in Table 1. The children were then given a special high-fat diet for one to two weeks. This diet had a ketogenic anti-ketogenic ratio of

3·5 : 1 as calculated from Shaffer's[12] data. This diet was similar to the one used by Brown and Graham[13] in their work on ketonæmia and ketonuria, in which they found in every case an increase in the blood acetone accompanied by a fall in the alkaline reserve.

As can be seen from Table 1 and Chart A (demonstrating one case and a composite curve) the glucose tolerance was markedly reduced during the ketogenic-diet periods. The tendency of the blood sugar to remain at a high level at the end of the two hour period is particularly striking though, in contradistinction to the true diabetic curve, it must be noted that the fasting blood-sugar level was always low.

TABLE 1.

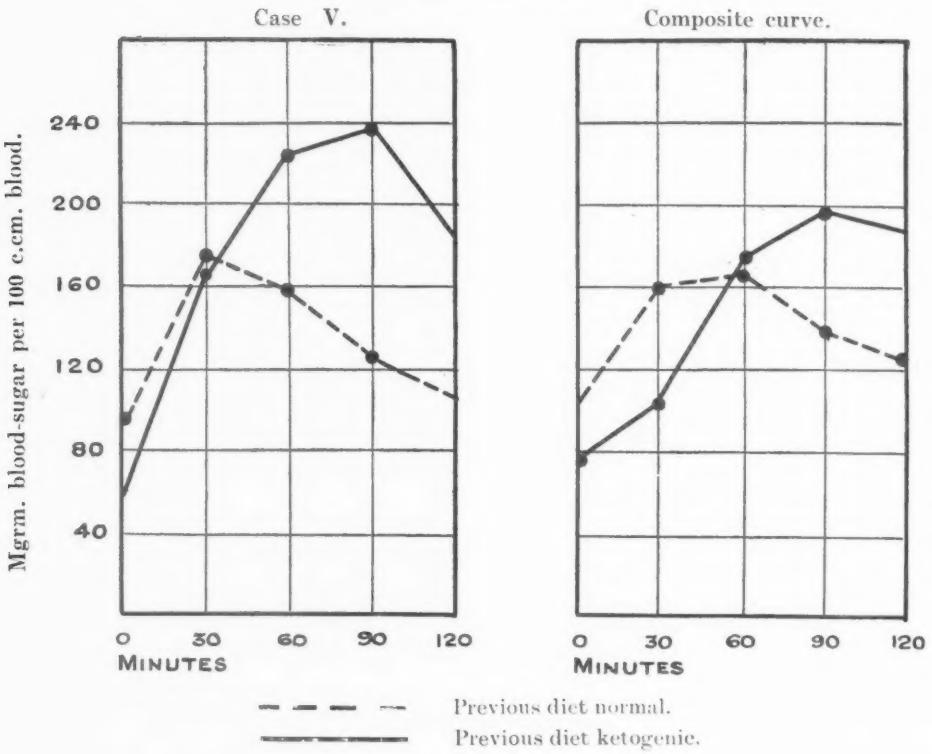
BLOOD-SUGAR CURVES AFTER 1 GRM. OF GLUCOSE PER KGRM. BODY WEIGHT.

Case	Wt. kgrm.	Amt. of Gluc. grm.	Diet	Duration of fast. hrs.	Percentage of glucose in blood.						Urine.
					Fasting level.	Minutes after glucose					
						30	60	90	120	150	
1	28	28	N	8	·106	·166	·204	·189	·162	—	Nil.
			K	15	·072	·072	·168	·201	·193	—	Acetone + ; No sugar
2	27	27	N	15	·109	·115	·137	·141	·125	—	Nil.
			K	15	·092	·082	·134	·211	·221	·231	No sugar : Acetone +
3	22	22	N	15	·095	·179	·159	·129	·113	—	Nil
			K	8	·072	·164	·224	·234	·179	·177	No sugar : Acetone +
4	28	28	N	15	·100	·125	·152	·109	·121	—	Nil.
			K	8	·062	·075	·148	·159	·162	—	No sugar : Acetone +
5	24	24	N	8	·119	·204	·196	·158	·111	—	Nil.
			K	8	·077	·134	·182	·221	·187	—	No sugar : Acetone +
6	27	27	N	8	·113	·137	·147	·141	·109	—	Nil.
			K	15	·072	·103	·159	·141	·162	—	No sugar: Acet. trace
7	25	25	N	15	·127	·181	·189	·123	·141	—	Nil.
			K	15	·100	·162	·218	·206	·177	—	Acetone + : No sugar
8	25	25	N	?	·097	·114	·093	·113	·113	—	Nil.
			K	?	·104	·191	·251	·247	·162	—	Acetone +

N. = Normal diet.
K. = Ketogenic diet.

CHART A.

BLOOD-SUGAR CURVES AFTER GLUCOSE.



Glucose tolerance after ammonium chloride.—The sugar tolerance of nine children, four of whom were also subjects of the previous test, was examined after the administration of ammonium chloride. The normal glucose tolerance was estimated in those not previously investigated, and thereafter the children were given ammonium chloride for varying periods of time. The details of the experiment are set out more fully below as each case comes to be discussed. The quantity of ammonium chloride given was approximately equivalent to the amount which Haldane[11] used. The children, who were more or less of the same weight, were all given 1 grm. of the drug in capsule form five times a day before meals.

The results were, however, so much less consistent than those obtained from the ketogenic diet that various changes in the diet and the duration of administration of the drug were made with a view to obtaining more uniform results, but it was found that those changes had no effect. The results are tabulated in Table 2.

Cases 1 and 7 were given ammonium chloride for four days and both showed an increased tolerance for glucose, the curve being lower and the value returning sooner to fasting than on normal diet. On ketogenic diet both these cases showed a reduced tolerance for glucose. That the condition of acidosis had been definitely established by the fourth day can be seen from

TABLE 2.

BLOOD-SUGAR CURVES AFTER THE ADMINISTRATION OF NH_4Cl.

Case.	Amt. of glucose grm.	Diet and drugs.	No. of days on am. chlor.	Percentage glucose in blood.					Urine.
				Fasting level.	Minutes after glucose. 30	60	90	120	
1	28	N	—	·106	·166	·204	·189	·162	Nil.
		N + NH_4Cl	4	·104	·144	·164	·104	·082	Nil.
2	27	N	—	·109	·115	·137	·141	·125	Nil.
		M + S + NH_4Cl	7	·113	·181	·211	·172	·141	Sugar + +
7	25	N	—	·127	·181	·189	·123	·141	Nil.
		O + NH_4Cl	4	·058	·154	·134	·077	·041	Nil.
8	25	N	—	·129	·181	·196	·141	·131	Nil.
		Milk	—	·100	·152	·177	·129	·104	Nil.
		N + NH_4Cl	8	·109	·207	·177	·122	·100	Nil.
		N + NH_4Cl	16	·104	·161	·157	·166	·095	Nil.
		N + NH_4Cl	24	·115	·209	·254	·164	·107	Nil.
9	20	N	—	·156	·186	·147	·162	·129	Nil.
		M + S + NH_4Cl	7	·134	·261	·206	·196	·181	Trace sugar
10	21	N	—	·077	·137	·157	·152	·113	Nil.
		M + S + NH_4Cl	13	·085	·134	·137	·152	·134	Nil.
11	16	N	—	·085	·129	160	·139	·113	Nil.
		N + NH_4Cl	8	·085	·209	·201	·117	·067	Nil.
12	26	N	—	·109	·175	·147	·134	·113	Nil.
		Milk	—	·084	·193	·206	·150	·063	Nil.
		N + NH_4Cl	8	·109	·172	·234	·189	·085	Nil.
		M + NH_4Cl	7	·077	·184	·189	·182	·109	Nil.
13	18	N	—	·095	·137	·177	·116	·100	Nil.
		N + NH_4Cl	6	·109	·149	·152	·129	·081	Nil.
		N + NH_4Cl	18	·092	·141	·157	·152	·113	Nil.
		N + NH_4Cl	24	·113	·152	·186	·162	·117	Nil.
		M + NH_4Cl	32	·109	·174	·204	·194	·121	Nil.
		Milk	—	·096	·132	·132	·077	·072	Nil.

N = Normal diet.

M = Milk diet equal to caloric requirements.

M + S = Milk and sugar equal to caloric requirements.

Table 3 which shows the change in the CO_2 content of the blood in three of the cases.

TABLE 3.

Case No. 2.	CO_2 Vol. %.
Normal.	68·2
4 days on NH_4Cl.	41·4
8 ,, ,, ,,	40·3
Case No. 7.	
Normal.	60·6
3 days on NH_4Cl.	45·1
6 ,, ,, ,,	41·8
9 ,, ,, ,,	43·4
13 ,, ,, ,,	45·0
Case No. 10.	
Normal.	66·7
9 days on NH_4Cl.	49·1
19 ,, ,, ,,	45·8

It is obvious that the acidosis produced by ammonium chloride had not in Cases 1 and 7 reduced the tolerance for glucose.

Cases 2, 9 and 10 were given for 10 days previous to the test, a milk diet plus 40 grm. of sugar daily, the diet containing an adequate caloric content for their respective weights. Then for seven days in Cases 2 and 9, and for 13 days in Case 10, ammonium chloride was administered, and the sugar tolerance then estimated. In Cases 2 and 9 a markedly reduced tolerance was noted and glycosuria occurred in both cases, though in Case 2 the hyperglycæmia was not as prolonged as that produced by the ketogenic diet. In Case 10 no change occurred.

Cases 11, 12 and 8 were given ammonium chloride for eight days, and Cases 11 and 12 showed a definite reduction and Case 8 a slight reduction in tolerance. At the end of 16 days of ammonium chloride administration Case 8 showed an increased tolerance for glucose though, as shown by Case 10, the acidosis from ammonium chloride lasts longer than this. Cases 12 and 13 were given, next, a milk diet without the addition of sugar but the administration of the drug was continued. Case 12 showed no change, but Case 13 gave a definitely higher curve than before, although not as high as that obtained on a ketogenic diet. After 32 days on the drug Case 13 showed little change in the tolerance for glucose.

Only two of the cases (No. 2 and 9) showed curves at all comparable to those found with ketogenic diet. In the others there was a slight reduction in the tolerance for glucose, but there was no delay in the return to fasting level, a feature which is so characteristic of the diabetic curve obtained on a high-fat diet.

These experiments show that compared with the disturbance which is the result of a high-fat low-carbohydrate diet the acidosis produced by ammonium chloride damages but slightly the ability of the organism to utilize carbohydrate.

In a case (A. F.) of severe clinical acidosis treated in the Royal Hospital for Sick Children the blood sugar (after glucose) was ·331 per cent. and the CO_2 was 30 vol. per cent. The next day when the acidosis had gone, the CO_2 being 72 vol. per cent., the blood sugar after glucose was still high, ·299 per cent., so that the return of the acid base balance to normal had not restored the ability of the tissues to utilize glucose.

It seems, therefore, that non-gaseous acidosis is not in itself the cause of the disturbance in the glycogenic function.

Action of insulin and adrenalin in ketosis.—There is a difference in the acidosis which is produced by ammonium chloride and that produced by a ketogenic diet. The latter is accompanied by acetonuria, acetone in varying amounts appearing in the urine throughout the period of administration of the drug. It has been shown that no matter how small the quantity of acetone in the urine there is an accompanying acetonæmia, and it may be that this acetonæmia plays a part in the disturbance of the metabolism. Von Noorden[14] observed that glycosuria and hyperglycæmia occurred after the administration of acetone; and Morris and Graham[15] found that rabbits, injected with 20 per cent. acetone, showed a slight increase in the sugar content of the blood.

Severinghaus[4] has put forward the suggestion that ketosis inhibits the production or the action of insulin, and it would seem from the above experiment that there may be grounds for this belief. This point was tested by the following experiments.

The subjects, whose reaction to glucose both on normal and ketogenic diets was known, were each given 5 units of insulin while in the post-absorptive state, and the blood sugar estimated 10, 30, 60, 90 and 120 minutes after the injection.

On normal diet 5 units of insulin produced a very slight fall in the blood sugar. The results are tabulated in Table 4 and Chart B. If the reaction to insulin on normal diet was slight, the response after ketogenic diet was striking. In all but one of the cases hypoglycæmia was marked and in three definite symptoms were noted.

The length of time the subject was on ketogenic diet had but little bearing on the reaction and Case 4 gave two practically parallel curves, though one was performed on the seventh day and the other on the twelfth day from the commencement of the diet. The resultant hypoglycæmia was but little influenced also by the level of the fasting blood sugar as is shown by the figures given in Table 5.

This fact has been commented upon by Macleod[16] who demonstrated in rabbits that the level of the blood sugar existing at the time of the injection

TABLE 4.

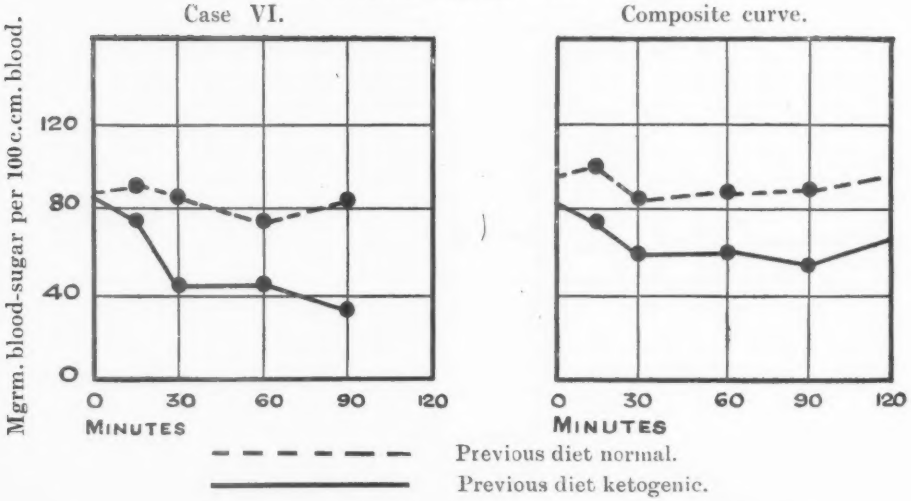
BLOOD-SUGAR CURVES AFTER INSULIN.

Case	Age yr.	Units of insulin	Diet	Percentage glucose in blood. Fasting level	Minutes after insulin: 10	30	60	90	120	150	Fall in blood sugar mgrm.	Urine
1	12	5	N	·104	·094	·100	·094	—	·089	—	10	Nil.
			K	·075	·060	·042	·042	·040	·064	—	35	Acetone + +
2	10	5	N	·107	·104	·087	·100	·109	—	—	20	Nil.
			K	·102	·083	·065	·069	·053	·055*	·030	72	Acetone + +
3	10	5	N	·103	·125	·100	·094	·100	—	—	(rise)	Nil.
			N	·082	·084	·075	·097	·072	·084	—	22	Nil.
			K	·067	·063	·067	·056	·063	·063	—	11	Acetone +
			K	·067	·077	·066	·058	·065	—	—	10	Acetone +
4	11	5	N	·090	·117	·104	·090	·094	—	—	(rise)	Nil.
			N	·104	·102	·067	·082	·082	—	—	37	Nil.
			K	·100	·091	·081	·077	·055	·069	—	45	Acetone +
5	12	5	N	·116	·100	·087	·089	·094	·104	—	39	Nil.
			K	·092	·094	·072	·077	075	·075	—	20	Acetone +
6	11	5	N	·082	·089	·084	·077	·082	—	—	5	Nil.
			K	·081	·072	·042	·042	·035	—	—	46	Acetone +
7	9	5	N	·089	·089	·077	·089	·085	—	—	12	Nil.
			K	·064	·058	·053	·052	·048	·043	—	21	
Composite Curve.			N	·097	·100	·086	·090	·092	—	—	9	—
			K	·081	·075	·059	·059	·061	—	—	27	—

* Hypoglycæmic symptoms. N = Normal diet. K = Ketogenic diet.

CHART B.

BLOOD-SUGAR CURVES AFTER INSULIN.



of insulin and the steepness of the initial fall in the blood sugar are not related unless the fasting level be very high when the descent becomes more rapid.

TABLE 5.

FALL OF BLOOD SUGAR AFTER INSULIN.

Case	Blood sugar		Case	Blood sugar	
	Fasting	Lowest value		Fasting	Lowest value
1	·075 mgrm. %	·040 mgrm. %	5	·092 mgrm. %	·072 mgrm. %
2	·102 ,, ,,	·030 ,, ,,	6	·081 ,, ,,	·035 ,, ,,
3	·067 ,, ,,	·056 ,, ,,	7	·064 ,, ,,	·043 ,, ,,
4	·100 ,, ,,	·055 ,, ,,			

Case 3, who reacted very slightly both on normal and on special diet, seemed to possess a tolerance for insulin shown by none of the others.

It is clear that the presence of ketonæmia as indicated by ketonuria does not inhibit the action of insulin. Since the action of adrenalin and insulin are so closely concerned in the metabolism of carbohydrate the action of adrenalin during the ingestion of a ketogenic diet was also investigated in the same cases.

The smallest quantity of adrenalin chloride (1/1,000 sol. B.W. & Co.) which caused a rise in the blood sugar of children of different ages has been worked out at the Royal Hospital for Sick Children by Dr. Isobel Mitchell. It was found that the quantity of adrenalin necessary depended on the age of the child (Table 6).

TABLE 6.

Age of child	Amount of adrenalin
1 year	1 minim
2 years	2 minims
3, 4, 5, 6, 7 years	3 ,,
8 years	4 ,,
9, 10, 11 years	5 ,,
12 years	6 ,,

In the work detailed below the amounts of adrenalin used were based on this standard. The injections were subcutaneous and the blood for the estimations was taken before and 10, 30, 60, 90 and 120 minutes after the injection.

TABLE 7.

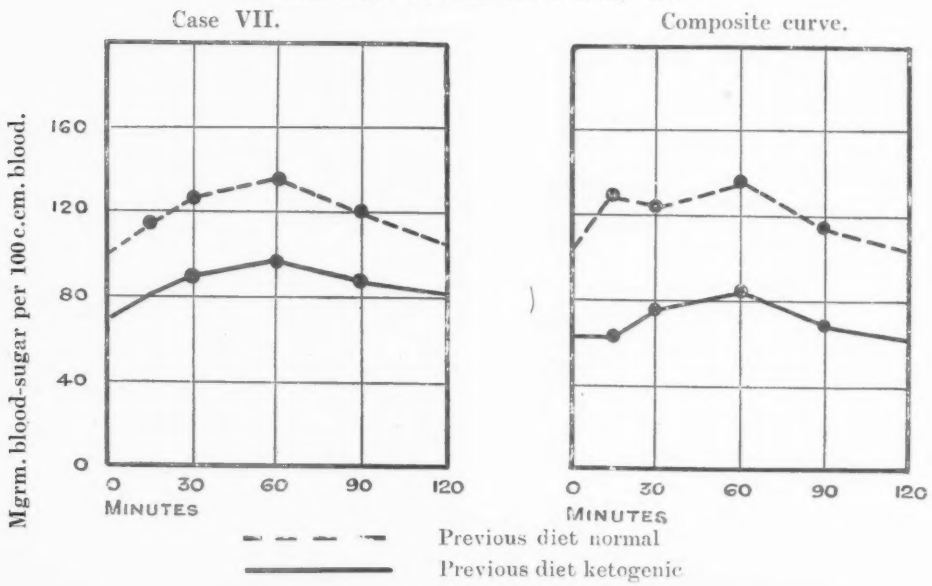
BLOOD-SUGAR CURVES AFTER ADRENALIN.

Case	Age yr.	Adrenalin. minim	Diet	Percentage mgrm. of blood sugar							Rise in blood sugar mgrm.	Urine
				Fasting level	Minutes after adrenalin							
					10	30	60	90	120	150		
1	12	6	N	·104	·104	·117	·132	·132	·100	—	28	Nil.
			K	·075	·075	·085	·100	·090	·072	—	25	Acetone + + +
2	10	5	N	·089	·100	·131	·122	·117	·089	—	42	Nil.
			K	·067	·077	·077	·067	·072	·100	·072	53	Acetone + + +
3	10	5	N	·084	·134	·107	·117	·105	·111	—	50	Nil.
			K	·077	·083	·077	·077	·117	·058	—	40	Acetone + +
4	11	6	N	·160	·116	·129	·132	·125	·116	—	32	Nil.
			K	·074	·043	·056	·060	·072	·081	—	—	Acetone + + +
			K	·084	·097	·117	·131	·164	—	—	47	Acetone +
5	12	6	N	·113	·123	·172	·191	·139	·125	—	78	Nil.
			K	·079	·102	·119	·129	·100	·089	—	50	Acetone + + +
6	11	6	N	·104	·129	·117	·117	·134	·122	—	30	Nil.
			K	·063	·067	·081	·089	·072	·089	—	26	Acetone + + +
7	9	5	N	·094	·125	·123	·134	·117	·104	—	40	Nil.
				·063	·064	·075	·084	·072	·064	—	21	Acetone + + +
Composite curve			N	·098	·119	·128	·135	·184	·109	—	37	Nil.
			K	·072	·081	·090	·097	·089	·079	—	25	

N = Normal diet. K = Ketogenic diet.

CHART C.

BLOOD-SUGAR CURVES AFTER ADRENALIN.



All seven cases, under ordinary dietary conditions, showed the normal response after the injection of adrenalin, the hyperglycæmia being appreciable and sustained for at least 1½ hours. The results obtained while the children were receiving ketogenic diet were quite different. The blood sugar did not rise so high above the fasting level nor was the hyperglycæmia so sustained, indicating that the release of glycogen was less than when the subjects were on ordinary diet. From these results it seems clear that the actions of insulin and adrenalin are definitely modified by ketogenic diet.

Discussion.

Our results show that the acidosis produced by the administration of ammonium chloride does not cause any notable disturbance of carbohydrate metabolism, while in that associated with ketosis there is a definite disturbance, manifested not only by sugar-tolerance tests but also by the reactions to insulin and adrenalin. Probably, then, acidosis in itself is not the disturbing factor. This conclusion is supported by the work of Ellis[17] who found that administration of sodium bicarbonate with ketogenic diet did not lessen the intolerance to glucose. It may be, however, that ketone bodies circulating in the blood are responsible for the alteration in sugar tolerance, but there is another possibility which requires consideration. In the production of ketosis it is necessary to reduce the carbohydrate intake to a minimum and consequently to reduce the store of carbohydrate in the liver and tissues, and it may be that the disturbance of carbohydrate metabolism which has been found to occur in subjects on ketogenic diet is due not to ketosis but to depletion of carbohydrate stores. Certain findings by other workers are worth considering in this connexion. Stewart and Rogoff[18] showed that prolonged action of insulin is not due to any inhibition of the adrenals since complete removal of these glands in rabbits did not affect the action of insulin. MacLeod and others[19] found that in rabbits the richer the glycogen content of the liver the more resistant were they to insulin. Lawrence[20] has pointed out that in patients suffering from diabetes mellitus insulin is much more effective when the glycogen store is low. From the work of Mann and Magath[21] and Burn and Marks[22] it can be concluded that the hyperglycæmia which occurs after the injection of adrenalin is dependent upon the amount of liver glycogen.

These findings suggest that the enhanced effect of insulin and the diminished action of adrenalin are due to depleted stores of carbohydrate rather than to the presence of ketonæmia. It would also seem fair to infer that the effect of ketogenic diet in producing an alteration in carbohydrate metabolism is due chiefly to the diminution in the glycogen content of the liver. If this be true it offers an explanation of the difference in the reaction to the acidosis produced by ammonium chloride and that induced by ketogenic diet.

Summary

The effect of ketogenic diet on the blood-sugar curve following glucose ingestion is to cause a rise greater than normal and a delay in the return to the fasting level. The fasting blood sugar is generally definitely lowered when the subject is on ketogenic diet.

Ammonium-chloride ingestion occasionally produces a change in the blood-sugar curve, but the change is much less marked than that produced by ketogenic diet.

The action of insulin is augmented and the effect of adrenalin diminished when the previous diet is ketogenic.

It is suggested that the alteration in the carbohydrate metabolism caused by ketogenic diet is not due to acidosis but to diminution in stores of carbohydrate produced by this diet.

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